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Direct Oral Anticoagulants for the Treatment of Venous Thromboembolic Events: Economic Evaluation

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Authors: Scott Klarenbach,[1] Karen Lee,[1] Michel Boucher,[2] Helen So,[1] Braden Manns,[1] Marcello Tonelli[3]

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[1] University of Alberta, Edmonton, Alberta
[2] CADTH, Ottawa, Ontario
[3] University of Calgary, Calgary, Alberta

Reviewers

Content Experts

These individuals kindly provided comments on this report, including the project scope, project protocol, included studies, and economic model and draft reports:

Marc Carrier, M.D., MSc, FRCPC
Senior Scientist, Clinical Epidemiology Program
Ottawa Hospital Research Institute
Associate Professor, Department of Medicine
University of Ottawa
Ottawa, ON, Canada

William H. Geerts, MD, FRCPC
Director, Thromboembolism Program
Consultant in Clinical Thromboembolism
Senior Scientist, Clinical Epidemiology and Health Services Research,
Sunnybrook Health Sciences Centre
Professor, Department of Medicine and Centre for Patient Safety,
University of Toronto
Toronto, ON, Canada

Agnes Y. Y. Lee, MD, MSc, FRCPC
Medical Director, Thrombosis Program
Associate Professor of Medicine, Division of Hematology
University of British Columbia and Vancouver Coastal Health
Diamond Health Care Centre
2775 Laurel Street, 10th floor
Vancouver, BC, Canada

Authorship

Scott Klarenbach participated in the conceptualization and design of economic evaluation, led the analysis and interpretation of the results, drafted the report, and conducted all revisions for the final report.

Karen Lee contributed to the project scope, reviewed the network meta-analysis (NMA) data used as inputs into the economic model, and reviewed various drafts and the final report.

Michel Boucher developed the health technology assessment project (including the clinical and economic evaluations). He was responsible for the oversight of the clinical evaluation that was the source of the clinical data for the economic evaluation. He was a contributor to the economic evaluation, which involved securing clinical experts, reviewing the NMA data used as inputs into the economic model, writing a portion of the Background section of the report, and reviewing drafts of the report.

Helen So participated in the conception and design of the economic model, analyzed data, generated model results, and drafted and revised the report.

Braden Manns participated in the conception and design of the economic evaluation, and participated in the analysis and interpretation of results and report revisions.

Marcello Tonelli participated in the conception and design of the economic evaluation, and participated in the analysis and interpretation of results and report revisions.
All authors approved the final draft report.

Contributors

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Conflicts of Interest

Dr. Agnes Lee received funding for educational lectures from Bayer, Boehringer Ingelheim, Pfizer, and Sanofi-Aventis. She received research funding and/or consulted for Bayer, Bristol-Myers Squibb, Daiichi Sankyo, LEO Pharma and Pfizer. She provided reviews and advice for the Guidelines and Protocols Advisory Committee for the Doctors of BC and the British Columbia Ministry of Health.

Dr. Marc Carrier received honorariums for speaking engagements from Sanofi-Aventis, Pfizer, Boehringer Ingelheim, LEO Pharma, and Bayer. He received research funding from LEO Pharma and Bristol-Myers Squibb and was a consultant for Scientific Advisory Board meetings for Sanofi-Aventis and LEO Pharma.

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No other conflicts of interest were declared.

Key Findings — Economic Evaluation

- Compared with low-molecular-weight heparin/vitamin K antagonist (LMWH/VKA), treatment of venous thromboembolism (VTE) with apixaban for an intended duration of three or six months is associated with an incremental cost-utility ratio (ICUR) of $170,000 to $222,000 per quality-adjusted life-year (QALY) gained, respectively. Other direct oral anticoagulants (DOACs), including dabigatran, edoxaban, and rivaroxaban, are dominated by apixaban or LMWH/VKA. Notably, rivaroxaban is associated with greater costs but fewer QALYs than LMWH/VKA.
- The major cost driver for DOACs is drug acquisition, which is far greater than VKA. The majority of the total drug acquisition costs of DOACs, whether in the three- or six-month treatment duration, occur after six months. Recurrent VTE is common, occurring in 30% to 50% of patients by 10 years, and is typically treated with extended-duration (lifelong) therapy. Re-initiation of therapy in patients with recurrent VTE accounts for the large drug acquisition costs over a lifetime horizon.
- The relatively small incremental QALYs with apixaban compared with LMWH/VKA (an additional seven to 11 days of perfect health) are due to the reduction in the risk of major bleeding when anticoagulation is used for extended treatment. However, the risk of major bleeding is not large with extended treatment, and intracranial hemorrhage, which is associated with significant morbidity, mortality, and increased health care costs, is less frequent than the other type of major bleeding (gastrointestinal bleeding).
- These results were generally robust to sensitivity analysis. Apixaban becomes more attractive compared with LMWH/VKA when there are substantial price reductions in drug acquisition costs, if admissions for VTE are substantially reduced, if resource use for VKA monitoring is large, or if the bleeding risk is at the upper end of its range. The relative rank ordering of DOACs did not change, although it is worth noting that differences in efficacy and safety among DOACs are not well studied.
- If the duration of DOAC use is constrained to a maximum of three or six months, so that any recurrent VTE is treated with LMWH/VKA, there are no differences in QALYs (differences in efficacy and safety are only present with extended but not acute therapy), and DOACs are associated with modest cost savings compared with LMWH/VKA. The increased drug acquisition costs with DOACs are offset by the monitoring costs of VKA, the costs of LMWH (although some DOACs are used with LMWH in the same manner as VKA), and reduction in index hospitalization cost. However, it may be challenging to operationalize this constraint, as patients with recurrent VTE who have previously been treated with a DOAC may prefer to continue or restart therapy with a previous treatment; a similar preference may hold for providers as well. Among DOACs, there are minor cost differences with the lowest costs associated with apixaban and rivaroxaban.

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Abbreviations

ASA	acetylsalicylic acid
ccNMA	Canadian Collaboration for Drug Safety, Effectiveness and Network Meta-Analysis
CI	confidence interval
CRNM	clinically relevant non-major
CTEPH	chronic thromboembolic pulmonary hypertension
DOAC	direct oral anticoagulant
DVT	deep vein thrombosis
EC	extracranial
IC	intracranial
ICH	intracranial hemorrhage
ICUR	incremental cost-utility ratio
INR	international normalized ratio
LMWH	low-molecular-weight heparin
LOS	length of stay
NMA	network meta-analysis
NOC	notice of compliance
OCCI	Ontario Case Costing Initiative
PE	pulmonary embolism
PTS	post-thrombotic syndrome
QALY	quality-adjusted life-year
VKA	vitamin K antagonist
VTE	venous thromboembolism

Background

Venous thromboembolic events (VTEs) include both deep vein thrombosis (DVT) and pulmonary embolism (PE). DVT can be associated with symptoms of pain, swelling, and erythema in the affected region (typically leg), and also can lead to late complications including post-thrombotic syndrome. The most serious sequela of DVT is embolization of the thrombus to pulmonary circulation (i.e., a PE), which may result in pulmonary insufficiency, respiratory failure, or death. Patients with one episode of VTE are at risk of recurrent VTE (DVT or PE), although this risk may vary depending on precipitating factors and clinical context.

VTEs represent an important disease burden in Canada; they are common and likely to increase with aging of the population.[1] The average annual incidence of VTE is one person per 1,000.[2] As there are 34.5 million persons living in Canada,[3] it may be projected that there are about 34,500 Canadians who are diagnosed with VTE each year.

The standard of care for patients diagnosed with DVT and/or PE has been systemic anticoagulation with heparin (low-molecular-weight heparin [LMWH], administered subcutaneously) followed by oral administration of vitamin K antagonists (VKAs), which are overlapped with LMWH until sufficient systematic anticoagulation with oral agents is achieved. The degree of systemic anticoagulation achieved with VKAs must be monitored using blood tests and dose adjustment to avoid inadequate anticoagulation (with attendant increased risk of recurrent VTE), or supratherapeutic anticoagulation (with increased risk of bleeding). Duration of therapy is dictated by the nature of the event and clinical context; current Canadian guidelines in general suggest either three months of treatment or long-term therapy.[4]

Recently, direct oral anticoagulants (DOACs) have been developed as an alternative to VKA for the treatment of VTE. Three DOACs are currently available in Canada: apixaban, dabigatran, and rivaroxaban. Rivaroxaban was the first DOAC to obtain its notice of compliance (NOC) for VTE, initially only for treatment of DVT (February 2012) and then for PE and prevention of recurrent DVT and PE (April 2013); dabigatran and apixaban were granted a NOC for VTE in June 2014 and November 2014, respectively.[5] The VTE clinical development program of a fourth DOAC (edoxaban) was recently completed, although this drug is not currently available in Canada; the submission for edoxaban is however currently being reviewed at Health Canada.[6] DOACs belong to two groups: direct thrombin inhibitors and direct factor Xa inhibitors (Table 1).

Table 1: Direct Oral Anticoagulants

Class	Drug	Manufacturer
Direct thrombin inhibitor	Dabigatran (Pradaxa)	Boehringer Ingelheim Canada Ltd.
Direct factor Xa inhibitor	Rivaroxaban (Xarelto)	Bayer Inc.
	Apixaban (Eliquis)	Pfizer Canada Inc./Bristol-Myers Squibb Canada
	Edoxaban (Lixiana)*	Daiichi-Sankyo

* Not yet available in Canada.

DOACs are given orally as a fixed dose, contrary to heparin products that require injection, and are not subject to the same laboratory monitoring requirements as oral VKAs. They are also less prone to dietary and drug interactions than VKAs. DOACs are, however, more expensive and are associated with more limited clinical experience compared with heparin products and VKAs. In particular, the dose of DOACs needs to be adjusted in case of renal dysfunction, and management of bleeding complications may be challenging given the lack of an agent to reverse DOACs' anticoagulant effect.

As the scope of indications approved for DOACs and the number of these drugs increase, the amount of pharmacological treatment options available for the treatment of VTEs expands. This not only impacts clinicians and patients, who have to make therapeutic choices based on patient characteristics and preferences, but also payers, as DOACs are more costly than VKA products.

Currently, several publicly funded drug programs in Canada provide reimbursement for DOACs, though some restrictions may apply, when used for post-orthopaedic surgery VTE prevention and for stroke prevention in patients with atrial fibrillation. Rivaroxaban is reimbursed by public payers for the treatment of VTE and the prevention of recurrent events; some provincial drug programs now also reimburse apixaban for these indications. As more DOACs receive their NOC for VTE, additional reimbursement decisions will need to be made.

In order to inform policy work and clinical decisions, a health technology assessment was undertaken by CADTH. For this project CADTH worked in partnership with the Canadian Collaboration for Drug Safety, Effectiveness and Network Meta-Analysis (ccNMA), funded by the Drug Safety and Effectiveness Network (DSEN) of the Canadian Institutes of Health Research (CIHR). The health technology assessment includes both a clinical and an economic evaluation. The clinical component was conducted by ccNMA, and the economic evaluation was conducted by CADTH. This report provides findings from the economic evaluation.

The economic evaluation was undertaken to inform the rational use of DOACs and ensure health care system sustainability; it aimed to determine the cost-effectiveness of anticoagulation treatment strategies for patients with VTE. This was done in close collaboration with ccNMA, which conducted a rigorous systematic review of randomized controlled trials and a network meta-analysis (NMA) used to inform the relative efficacy and safety in the economic evaluation. Findings from the economic evaluation are presented in this report; the results of the clinical evaluation are available at: https://www.ottawaheart.ca/researchers/resources-services/core-facilities/cardiovascular-research-methods-centre[7]

Primary Economic Evaluation

The objective of the economic evaluation is to determine the incremental cost-effectiveness of direct oral anticoagulants (rivaroxaban, apixaban, edoxaban, dabigatran) compared with standard of care (LMWH followed by oral VKA) for patients newly diagnosed with DVT/PE within the Canadian health care system for various durations of therapy (three months, six months, and lifelong).

Methods

Type of Economic Evaluation

As VTE and its treatment impacts both quality of life and mortality, a cost-utility analysis, where health outcomes are quantified using quality-adjusted life-years (QALYs), was used. Incremental costs and QALYs of alternate treatment strategies were determined.

Target Population

The target population for assessment of treatment duration of three or six months is based on the weighted average of characteristics of adult patients who were enrolled in randomized clinical trials included in the clinical systematic review for acute treatment (less than 12 months; included trials examined three, six, and 12 months' duration) of VTE.[7] Simulated patients had an average age of 56 years old, 57% were male, with 57% presenting with DVT and 43% presenting with PE (± DVT). As noted within the studies, 60% to 90% had an unprovoked VTE. It is assumed that patients enrolled in clinical trials had characteristics similar to Canadian patients presenting with VTE.

The target population for assessment of lifelong treatment duration is based on characteristics of patients enrolled in randomized trials of extended-duration therapy (trial duration one to 4.5 years after VTE).[7] Patients had an average age of 57 years, 58% were male, and 65% presented with DVT (35% PE ± DVT) (DOAC and VKA trials only).

Duration of treatment for three months, six months, and lifelong were examined.

Treatment Comparators

The following treatments were considered in the model:

- Standard of care, consisting of systemic anticoagulation with LMWH administered subcutaneously, with simultaneous initiation of oral administration of VKAs, which are overlapped with LMWH until sufficient systematic anticoagulation with oral agents is achieved. The dose and duration of LMWH was based on trials identified and included in the clinical review.[7]
- DOACs examined in the clinical systematic review, including factor Xa inhibitors (rivaroxaban, apixaban, edoxaban) and direct thrombin inhibitors (dabigatran). The dose and frequency of each DOAC were based on trials included in the clinical review. Initial administration of dabigatran and edoxaban is overlapped with LMWH in a similar fashion to VKA; apixaban and rivaroxaban therapy begins with loading doses for seven and 21 days, respectively.

- For lifelong treatment, VKAs were also compared to antiplatelet drugs (acetylsalicylic acid [ASA]) as a comparator.

Table 2: Treatment Comparators

Treatment	Strategy
LMWH/VKA	Enoxaparin 1 mg/kg BID (initial ~7 days) and adjusted dose warfarin
Dabigatran	Enoxaparin 1 mg/kg BID (initial ~7 days) and dabigatran 150 mg BID
Edoxaban	Enoxaparin 1 mg/kg BID (initial ~7 days) and edoxaban 60 mg QD
Apixaban*	Apixaban 10 mg BID x 7 then 5 mg BID (extended therapy > 6 months 2.5 mg BID)
Rivaroxaban	Rivaroxaban 15 mg BID x 21 days then 20 mg QD
ASA	ASA 100 mg QD (extended therapy only)

ASA = acetylsalicylic acid; BID = twice daily; LMWH = low-molecular-weight heparin; QD = once daily; VKA = vitamin K antagonist.
* Doses of both 2.5 mg and 5 mg twice daily of apixaban have been studied for extended therapy, and both are examined.
Note that the acute treatment for both extended therapy dosing strategies is the same (loading dose then 5 mg twice daily).
Note: Alternate LMWHs include enoxaparin 1.5 mg/kg once daily, dalteparin 200 U/kg once daily, and tinzaparin 175 U/kg once daily.

Audience and Perspective

The target audience for this report includes provincial and regional drug plans and ministries of health in Canada.

The analysis was conducted from a Canadian Ministry of Health perspective, consistent with CADTH guidelines for conduct of economic evaluations.[8]

There may be minor considerations with respect to patient productivity as it relates to international normalized ratio (INR) testing, as well as patient preference regarding venipuncture for blood testing, dietary adherence (to avoid fluctuations in vitamin K intake) and dose adjustments with VKA. Patient productivity is likely to be minor and was not incorporated into the analysis; preferences are included in quality-of-life considerations.

Time Horizon

As clinical and economic consequences of VTE and its treatment persist indefinitely, a lifetime time horizon (20 years) was adopted. Alternate time horizons were assessed in sensitivity analysis.

Discount Rate

Costs and benefits were discounted at 5%, and rates of 0% and 3% were tested in sensitivity analysis.[8]

Modelling

A Markov model was created to examine a cohort of patients presenting with and treated for VTE. Patients may either present with DVT only, or PE (± DVT). The cohort is followed from presentation and initiation of treatment over their lifetime, regardless of duration of anticoagulation therapy.

The historical standard of care is characterized in the model with patient presentation of index VTE and commencement of treatment with LMWH plus VKA (oral warfarin). For each one-month cycle during treatment, patients may transition through various health states related to VTE and its treatment. Acute events include:

- recurrent VTE that is either DVT or PE (± DVT)
- major bleeds, which include intracranial (IC) or extracranial (EC) bleeding
- clinically relevant non-major (CRNM) bleeds.

Other events including myocardial infarction, ischemic stroke, and non–central nervous system systemic embolism are not included in the model, as these are uncommon events and available data does not suggest differences in probability of occurrence by treatment strategy.

Long-term health states are also included in the model:

- postthrombotic syndrome (PTS) in patients with DVT
- chronic thromboembolic pulmonary hypertension (CTEPH) in patients with PE
- post-stroke IC bleed.

Venous Thromboembolism (Deep Vein Thrombosis or Pulmonary Embolism)

For the index event or recurrent VTE, health care resources were used for investigation and management as an in-patient (if admitted to hospital) or outpatient. In the short-term treatment model, patients are treated with systemic anticoagulation for three or six months, after which anticoagulation therapy ceases. If a patient develops a recurrent VTE at any time, that patient incurs the same costs and health consequences, and will subsequently be treated with lifelong anticoagulation. For apixaban, extended therapy may be either 5 mg or 2.5 mg twice daily.

Major Bleeding

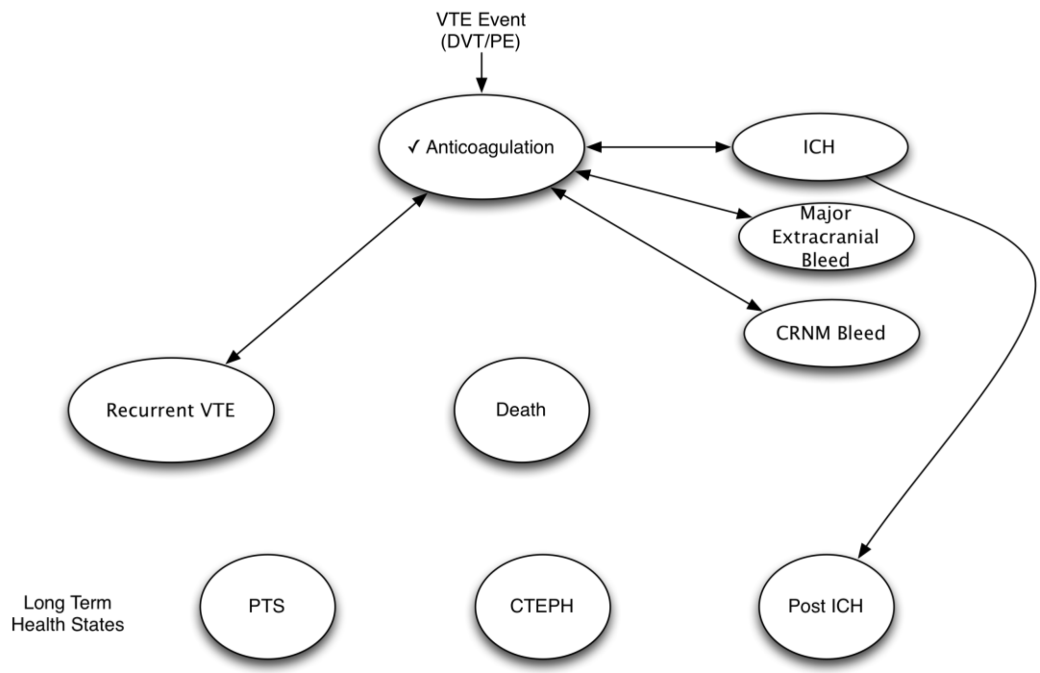
Major bleeding is further subclassified into either major extracranial or intracranial hemorrhage (ICH). The costs and consequences of major extracranial bleeding are assumed to be similar to major gastrointestinal bleeding, based on feedback from clinical experts. Extracranial bleeding is associated with acute costs as well as long-term health care resource utilization for attendant disability.

Postthrombotic Syndrome and Chronic Thromboembolic Pulmonary Hypertension

A subset of patients will have chronic consequences of their VTE event, which are associated with health care costs and impact on health. These states are incorporated, although as there is no difference in recurrent VTE risk by treatment strategy or evidence to suggest type of treatment influences the probability of developing PTS or CTEPH, inclusion of these states will have no impact on incremental health or health care costs.

The conceptual design of the model is detailed in Figure 1. The model assumes no difference in the consequences (health impact or cost) of events by treatment strategy alone, only by the health state.

Figure 1: Conceptual Design of Economic Model



CRNM = clinically relevant non-major; CTEPH = chronic thromboembolic pulmonary hypertension; DVT = deep vein thrombosis; ICH = intracranial hemorrhage; PE = pulmonary embolism; PTS = postthrombotic syndrome; VTE = venous thromboembolism.

The following model assumptions were made:

- It is assumed that patients who experience a major bleeding event will have anticoagulation therapy interrupted with a duration informed by Canadian clinical experts. Patients experiencing a bleeding event will temporarily cease anticoagulation therapy:
  - ICH: all patients stop anticoagulation for two weeks; 10% discontinue permanently
  - Major extracranial bleed: all patients stop anticoagulation for one week, then resume
  - CRNM bleed: all patients stop anticoagulation for four days, then resume.
- The risk of recurrent VTE is greatest in the first six months, and is reduced in subsequent periods (obtained from "short-term" trials and "extended" trials, respectively).
- Patients experiencing recurrent VTE will accrue the same costs and disutility as for an index VTE event. They will be treated with anticoagulation indefinitely. The baseline probabilities and hazard ratios from "extended"-duration studies will be used for these patients while on lifelong treatment. The type of anticoagulation used for lifelong treatment in patients with recurrent VTE will be the same as anticoagulation treatment for the index event.

Additional assumptions are provided in Table 3.

Table 3: Additional Model Assumptions

Patients enrolled in RCTs identified in clinical review are representative of Canadian patients with VTE.
A patient can experience any event within a cycle regardless of that patient's previous history, although previous history may affect the likelihood of such an event.
The relative efficacy of treatments is assumed to maintain when patients are on treatment.
The disutility from events other than IC bleeds, PTS, and CTEPH is temporary.
The cost of events other than IC bleeds, PTS, and CTEPH occurs only within the cycle when they occur.
There are long-term costs associated with IC bleeds, PTS, and CTEPH, which continue until death.
The long-term costs and utility for patients with a previous IC bleed are equivalent to outcomes for hemorrhagic strokes.
The costs and disutilities associated with bleeding events are not modified by the type of anticoagulation therapy.
For extended therapy treatment (lifelong) once a patient has an IC bleed, the patient will not experience future bleeding or recurrent VTE events.
The proportion of VTE events that are DVT vs. PE (± DVT) are the same for the index VTE (acute trials) as for recurrent VTE events.
The use of inferior vena cava filters that are rarely used in patients with severe bleeding but who are at high risk of recurrent VTE and complications are not considered in the model.

DVT = deep vein thrombosis; CTEPH = chronic thromboembolic pulmonary hypertension; IC = intracranial; PE = pulmonary embolism; PTS = postthrombotic syndrome; RCT = randomized controlled trial; vs. = versus; VTE = venous thromboembolism.

Mortality

Patients may also transition to the death state from any health state. All-cause mortality for the first six months was informed by survival data from included trials in the systematic review conducted for the acute phase.[7] After six months, all-cause mortality was informed by an observational study of patients with VTE followed for 10 years, which incorporates disease-specific mortality.[9] Patients experiencing a clinical event have an increased risk of death, informed by the mortality risk for these events as determined from the clinical systematic review, or, when not available, from literature sources.[9,10] Events that temporarily increase the risk of death include PE, IC bleed, and major EC bleed; CTEPH is associated with increased long-term mortality.

Baseline Probabilities and Relative Efficacy and Safety

The baseline probabilities for clinical events were obtained from the clinical review for the standard of care strategy (LMWH followed by VKA), where the probability and 95% confidence interval (CI) of an event occurring over various time frames was estimated using a Poisson model.[7] The probability of an event for a DOAC strategy was informed by applying the hazard ratio for the strategy compared with standard of care (LMWH/VKA) as determined by the NMA (below). Baseline probabilities and hazard ratios for the first six months of treatment (either three- or six-month treatment models) were obtained from short-term trials in the clinical review (Table 4); probabilities and hazard ratios after six months were obtained from “extended” therapy trials (Table 5). Other probabilities, including event-related probabilities, are shown in Table 6. A directed literature search was conducted to determine the probabilities of events not captured in the clinical review.

Table 4: Baseline Probabilities in Short-Term Treatment Model (Three to Six Months)

Variable Description	Base Estimate	Lower 95% CI	Upper 95% CI	Probability Distribution	Source	Comment
Month 0 to 6 with LMWH/VKA (probability over **3 months**)						
Probability of rVTE (on-treatment)	0.010	0.009	0.011	Beta (6 mo: 396/13,563)	NMA (acute)	
Probability of major bleed (EC or IC bleed)	0.0068	0.0059	0.0078	Beta (6 mo: 254/13,563)	NMA (acute)	
Proportion of major bleed that is IC bleed	0.165	-	-	Beta (42/254)	NMA (acute)	
Probability of CRNM bleed	0.0819	-	-	Beta (1,111/13,563)	Weighted average from acute trials	
Probability of death	0.0080	0.0071	0.0091	Normal	NMA (acute)	
Probability of rVTE (off-treatment)	0.0263	0.0213	0.0312	Normal	NMA (extended)	Prandoni[10] (0.0126)

CI = confidence interval; CRNM = clinically relevant non-major; EC = extracranial; IC = intracranial; LMWH = low-molecular-weight heparin; mo = month; NMA = network meta-analysis; rVTE = recurrent venous thromboembolism; VKA = vitamin K antagonist.

Table 5: Baseline Probabilities in Long-Term Treatment Model (After 6 months)

Variable Description	Base Estimate	Lower 95% CI	Upper 95% CI	Probability Distribution	Reference	Comment
Month 6+ with VKA (probability over **1 year**)						
Probability of rVTE (off-treatment)	0.101	0.0827	0.119	Normal	NMA (extended)	Prandoni[10] (0.0126)
Probability of rVTE (on-treatment)*	0.00938	0.00266	0.03627	Normal	NMA (acute)	
Probability of major bleed*	0.01201	0.00510	0.03045	Normal	NMA (acute)	
Probability of death	0.033	-	-	Normal	Schulman[9]	

CI = confidence interval; NMA = network meta-analysis; rVTE = recurrent venous thromboembolism; VKA = vitamin K antagonist.

Table 6: Event-Related Probabilities

Variable Description	Base Estimate	Lower 95% CI	Upper 95% CI	Probability Distribution	Source	Comment
Probability that rVTE is DVT (vs. PE)	0.57			Beta (185/396)	NMA (Acute)	
Probability that major bleed is ICH	0.165			Beta (42/254)	NMA (Acute)	
Probability of death for PE	0.0377	0.0110	0.0838	Beta (6/159)	NMA (Acute)	
Probability of PTS	0.081	00.058	0.104	Beta (28/528)	Prandoni[10]	For DVT
Probability of CTEPH (3 month)	0.0016	0.001	0.002	Beta (4/320)	Miniati[11]	For PE
Probability of death for IC bleed	0.436	0.365	0.507	Beta (82/188)	Linkins[12]	
Probability of death for EC bleed	0.039	0.027	0.054	Beta (27/689)	Linkins[12]	
Probability of death for CTEPH	0.0248	0.021	0.029	Normal	Condliffe[13]	

CI = confidence interval; CRNM = clinically relevant non-major; CTEPH = chronic thromboembolic pulmonary hypertension; DVT = deep vein thrombosis; EC = extracranial; IC = intracranial; ICH = intracranial hemorrhage; LMWH = low-molecular-weight heparin; mo = month; NMA = network meta-analysis; PE = pulmonary embolism; PTS = postthrombotic syndrome; rVTE = recurrent venous thromboembolism; VKA = vitamin K antagonist; vs. = versus.

Relative Efficacy and Safety

Treatment effects are based on data from a NMA to determine the relative efficacy and safety of alternate treatment strategies.[7]

The relative efficacy of acute treatment strategies (three- and six-month durations) was informed by a NMA comparing DOACs with LMWH/VKA. As reported in the clinical report, most efficacy and safety estimates in the NMA of acute treatment crossed unity (with large credible intervals) for all comparisons. In the absence of evidence of statistically significant differences, the hazard ratios in the model were set to 1.0 in the base case — for recurrent VTE, major bleeding including IC and EC bleeding, and CRNM bleeding (not an outcome in the clinical review but assumed to be similar between treatments). The point estimate and 95% credible intervals were used in the probabilistic sensitivity analysis (Table 7).

Table 7: Relative Efficacy and Safety (Hazard Ratio) Compared With Low-Molecular-Weight Heparin/Vitamin K Antagonist (Short-Term Treatment)

Variable Description	Reference Case	Point Estimate (PSA)	Lower 95% CrL	Upper 95% CrL	Probability Distribution
Hazard ratio for recurrent VTE					
Dabigatran	1.0	1.10	0.42	2.94	Lognormal
Rivaroxaban	1.0	0.98	0.37	2.52	Lognormal
Edoxaban	1.0	0.89	0.23	3.53	Lognormal
Apixaban	1.0	0.85	0.21	3.15	Lognormal
Hazard ratio for major bleed					
Dabigatran	1.0	0.75	0.28	1.96	Lognormal
Rivaroxaban	1.0	0.54	0.22	1.39	Lognormal
Edoxaban	1.0	0.85	0.23	3.07	Lognormal
Apixaban	1.0	0.31	0.08	1.18	Lognormal

CrL = credible interval; PSA = probabilistic sensitivity analysis; VTE = venous thromboembolism.
Source: Clinical Review Report — NMA[7]

Relative safety and efficacy for extended treatment (lifelong anticoagulation) was similarly informed from the NMA for extended-duration DOAC compared with VKA. In outcomes where no statistically significant difference was found between a DOAC and VKA, the hazard ratio was set as 1.0 in the reference case and, as above, the point estimate and 95% credible intervals were assessed in probabilistic sensitivity analysis (Table 8).

In the initial analysis, differences in efficacy and safety were found for the outcome of major bleeding where compared with VKA, rivaroxaban was associated with an increased hazard ratio (7.04; 95% CI, 1.34 to 79.20), and apixaban was associated with a lower risk of bleeding for both the 2.5 mg and 5.0 mg doses (0.23; 95% CI, 0.01 to 0.87 and 0.10; 95% CI, 0.00 to 0.41, respectively). The pre-specified model outcome of recurrent VTE with DOACs did not differ from LMWH/VKA; however, when individual outcomes of DVT or PE were examined, rivaroxaban was associated with an increased risk of DVT (hazard ratio 9.58; 95% CI, 1.001 to 167.10) and was assessed in sensitivity analysis.

Table 8: Relative Efficacy and Safety (Hazard Ratio) Compared With Low-Molecular-Weight Heparin/Vitamin K Antagonist (Extended Treatment) — Reference Case

Variable Description	Reference Case	PSA	Lower 95% CrL	Upper 95% CrL	Probability Distribution
Hazard ratio for rVTE					
Dabigatran	1.0	1.19	0.22	4.80	Lognormal
Rivaroxaban	1.0	2.17	0.17	19.64	Lognormal
Edoxaban	1.0	NA	NA	NA	Lognormal
Apixaban 2.5	1.0	2.17	0.18	19.30	Lognormal
Apixaban 5	1.0	2.19	0.19	19.43	Lognormal
ASA	7.41	7.41	1.00	41.48	Lognormal
Hazard ratio for major bleed					
Dabigatran	1.0	0.58	0.19	1.19	Lognormal
Rivaroxaban	7.04	7.04	1.34	79.20	Lognormal
Edoxaban	1.0	NA	NA	NA	Lognormal
Apixaban 2.5	0.23	0.23	0.01	0.87	Lognormal
Apixaban 5	0.10	0.10	0.00	0.41	Lognormal
ASA	1.0	0.19	0.04	9.63	Lognormal

ASA = acetylsalicylic acid; CrL = credible interval; LMWH = low-molecular-weight heparin; NA = not assessed; PSA = probabilistic sensitivity analysis; rVTE = recurrent venous thromboembolism; VKA = vitamin K antagonist.
Source: Clinical Review Report — NMA.[7]

The NMA for major bleeding is not robust, as there are zero numerators (i.e., zero events) in some groups of the evidence network (rivaroxaban), resulting in large credible intervals. In light of this, alternate approaches to analyzing the clinical data were considered in the clinical report. An analysis in the clinical report[7] attempts to explore this where all studies with a zero count were removed, except for the EINSTEIN-EXT study. In order to retain the rivaroxaban group, the event count was adjusted to one in the placebo group, retaining four in the rivaroxaban group. The "alternate" results were explored in sensitivity analysis (Table 9).

Table 9: Alternate Hazard Ratios for Major Bleed (Scenario Analysis)

Variable Description	Reference Case	PSA	Lower 95% CrL	Upper 95% CrL	Probability Distribution
Dabigatran	0.52	0.58	0.25	0.90	Lognormal
Rivaroxaban	1.0	0.73	0.21	12.78	Lognormal
Edoxaban	1.0	NA	NA	NA	Lognormal
Apixaban 2.5	0.10	0.10	0.014	0.44	Lognormal
Apixaban 5	0.018	0.018	0.0032	0.34	Lognormal
ASA	1.0	0.091	0.0039	4.67	Lognormal

ASA = acetylsalicylic acid; CrL = credible interval; NA = not assessed; PSA = probabilistic sensitivity analysis.
Note: Alternate hazard ratios to account for abnormalities in the evidence network, all studies with a zero count were removed, except for the EINSTEIN-EXT study. In order to retain the rivaroxaban group, the event count was adjusted to one in the placebo group (keeping four in the rivaroxaban group).
Source: Clinical Review Report — NMA.[7]

In the extended treatment comparison of VKA versus antiplatelet agents, ASA was associated with an increased hazard ratio of recurrent VTE (7.41; 95% CI, 1.00 to 41.48).

Utility

Each model state was assigned a utility weighting adjusted to account for cycle lengths. In the reference case, data from a Canadian study[14] that determined utility-based quality of life in 215 patients with a history of VTE using the standard gamble interview (Table 10) was used. The median utility values for acute DVT and PE, major intracranial bleed, and gastrointestinal bleed (major extracranial bleed) were used for each of these health states, and the interquartile range informed the range used in sensitivity analysis. The duration of utility impact was assumed to be one month for acute DVT and PE, one week for major extracranial bleeding (similar to gastrointestinal bleed), and permanent impact for major intracranial bleed.[14] Utility values for patients not experiencing an acute event or long-term consequences of a disease or treatment-related event were assigned a utility score based on Canadian population norms.[15] The utility of other long-term health states including PTS, CTEPH, and ICH were informed using a focused literature search (Table 10); a brief description of studies is provided in Table 11.

The analysis assumed that utility values for each health state were not modified by the type of treatment (LMWH/VKA versus DOAC). There has been speculation that the consequences of bleeding may be greater with DOACs given the lack of a specific antidote. While there is no evidence to support this, lower quality of life in surviving patients is tested in sensitivity analysis. Theoretically, quality of life may differ by treatment strategy, as VKA treatment requires venipuncture for INR assessment, dosing adjustment, and following dietary recommendations, none of which is required for DOAC therapy. However, a recent study comparing quality of life (using EuroQol 5-Dimensions Questionnaire [EQ-5D] and visual analogue scale) for patients with atrial fibrillation without an outcome event (e.g., stroke, bleed) over one year treated with either VKA or dabigatran found no difference in utility scores.[16] As such, no difference in utility by treatment was assumed in the analysis.

Table 10: Utility Values for Health States

Variable Description	Base Estimate	Lower	Upper	Distribution	Reference
Population norm	0.920	0.920	0.920	-	Maddigan 2005[15]
DVT* (1 mo)	0.810	0.550	0.940	Normal	Hogg 2013[14]
PE* (1 mo)	0.750	0.450	0.910	Normal	Hogg 2013[14]
Severe PTS*	0.930	1.000	0.760	Normal	Lenert 1997[17]
EC bleed* (1 wk)	0.650	0.150	0.860	Normal	Hogg 2013[14]
IC bleed*	0.150	0.000	0.650	Normal	Hogg 2013[14]
Post IC bleed	0.713	0.702	0.724	Normal	Rivero-Arias 2010[18]
CTEPH	0.560	0.528	0.592	Normal	Meads 2008[19]

CTEPH = chronic thromboembolic pulmonary hypertension; DVT = deep vein thrombosis; EC = extracranial; IC = intracranial; mo = month; PE = pulmonary embolism; PTS = postthrombotic syndrome; wk = week.
* Applied to population norm utility value either indefinitely or for the anticipated duration of disutility in parentheses.

Table 11: Description of Studies Informing Utility Values

Variable Description	Reference	Population	Method	Country
Population norm	Maddigan 2005[15]	1996-1997 Canadian National Population Health Survey control group (n = 53,137)	ANCOVA to compare overall HUI3 scores	Canada
DVT PE EC bleed IC bleed	Hogg 2013[14]	215 lower extremity DVT or PE patients	Standard gamble	Canada
SA: DVT PE EC bleed IC bleed	Locadia 2004[20]	124 VTE patients treated with VKA	Time trade-off	Netherlands
Severe PTS	Lenert 1997[17]	30 healthy women between ages of 20 and 40	VAS from scenario describing PTS	US
Post IC bleed	Rivero-Arias 2010[18]	The Oxford Vascular Study (population-based cohort, n = 2,425)	EQ-5D	UK
CTEPH	Meads 2008[19]	Pulmonary hypertension patients with CTEPH (n = 308/869)	CAMPHOR QoL	UK

ANCOVA = analysis of covariance; CAMPHOR = Cambridge Pulmonary Hypertension Outcome Review; CTEPH = chronic thromboembolic pulmonary hypertension; DVT = deep vein thrombosis; EC = extracranial; EQ-5D = EuroQol 5-Dimensions Questionnaire; HUI3 = Health Utilities Index Mark 3; IC = intracranial; PE = pulmonary embolism; PTS = postthrombotic syndrome; QoL = quality of life; SA = sensitivity analysis; VAS = visual analogue scale.

Resource Utilization

Drug Costs

Drug cost per day is determined using provincial formulary costs and recommended dosing for the duration of its use (Table 12). Pricing information for edoxaban is not yet available, and was assumed to have a similar daily cost of other DOACs. An 8% markup and $7 dispensing fee every three months was applied. Actual drug acquisition costs may be lower due to drug plan negotiations with the manufacturer, and was tested in sensitivity analysis.

Table 12: Drugs for the Treatment and Prevention of Recurring Venous Thromboembolism

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Daily Use	Average Daily Drug Cost ($)
Apixaban (Eliquis)	2.5 mg 5.0 mg	Tablet	1.6000	*Treatment of acute DVT ± PE*: 10 mg BID x 7 days, then 5 mg BID *Continued prevention of recurrent DVT +/ PE*: 2.5 mg BID after at least 6 months of treatment	First 7 days 6.40 Thereafter 3.20
Rivaroxaban (Xarelto)	10 mg 15 mg 20 mg	Tablet	2.8400	15 mg twice daily for 1st three weeks, then 20 mg daily for continued treatment and prevention	First 3 weeks: 5.68 Thereafter: 2.84
Dabigatran (Pradaxa)	75 mg 110 mg 150 mg	Capsule	1.6000 1.6000 1.6000	150 mg twice daily following treatment with a parenteral anticoagulant for 5 to 10 days	3.20[a]
Low-Molecular-Weight Heparins[b]					
Dalteparin sodium (Fragmin)	2,500 IU/0.2 mL 5,000 IU/0.2 mL 7,500 IU/0.3 mL 10,000 IU/0.4 mL 12,500 IU/0.5 mL 15,000 IU/0.6 mL 18,000 IU/0.72 mL	Syringe	5.3460 10.6910 16.0340 21.3820 26.7260 32.0700 38.4840	200 IU/kg SC once daily for approximately 5 days	32.07[c]
Enoxaparin sodium (Lovenox)	30 mg/0.3 mL 40 mg/0.4 mL 60 mg/0.6 mL 80 mg/0.8 mL 100 mg/1 mL 100 mg/ mL 120 mg/0.8 mL 150 mg/1 mL	Syringe Syringe Syringe Syringe Syringe 3 mL vial Syringe Syringe	6.3600 8.4800 12.7200 19.9600 21.2000 63.6000 25.4400 31.8000	1 mg/kg SC twice daily for approximately 7 days	39.92[c]
Nadroparin calcium (Fraxiparine)	0.3 mL 0.4 mL 0.6 mL 0.8 mL 1.0 mL	9,500 anti-Xa IU/mL Syringe	9.1290	171 anti-Xa IU/kg SC once daily for up to 10 days	18.26[c]
	0.6 mL 0.8 mL 1.0 mL	19,000 anti-Xa IU/mL Syringe	18.2580		
Tinzaparin sodium (Innohep)	2,500 IU/0.25 mL 3,500 IU/0.35 mL 4,500 IU/0.45 mL 10,000 IU/0.5 mL 14,000 IU/0.7 mL 18,000 IU/0.9 mL	Syringe	4.6800 6.5450 8.4170 18.5580 26.7490 34.3880	175 anti-Xa IU/kg SC once daily, average duration of 7 days	26.75[c]

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Daily Use	Average Daily Drug Cost ($)
	20,000 IU/2 mL 40,000 IU/2 mL	Vial	37.0980 75.3600		22.72[c]
Other Anticoagulants					
Warfarin (generic)	1 mg 2 mg 2.5 mg 3 mg 4 mg 5 mg 10 mg	Tablet	0.0796 0.0841 0.0674 0.1043 0.1043 0.0675 0.1211	Usual maintenance: 2 mg to 10 mg daily	0.07 to 0.12
ASA[d]	325 mg	Tablet	0.02	100 mg daily	0.20

BID = twice daily; DVT = deep vein thrombosis; IU = international units; PE = pulmonary embolism; SC = subcutaneously.
[a] Ontario Drug Benefit list price for the prevention of stroke and systemic embolism in at-risk patients with non-valvular atrial fibrillation; dabigatran had not been submitted for this indication to the CADTH Common Drug Review at the time of the apixaban review (although it has a Notice of Compliance form Health Canada for this indication).
[b] Concomitant treatment with warfarin is normally started immediately. Treatment with LMWHs should be continued until the levels of the prothrombin complex factors have decreased to a therapeutic level, in general for approximately 5 to 10 days.
[c] Assumes 70 kg patient weight.
[d] Drug plans do not currently cover 100 mg ASA, only 325 mg. It was assumed that if 100 mg was used, the price would be similar to 325 mg.
Source: Ontario Drug Benefit list prices (December 2014) unless otherwise indicated.

Index Event

Information on index hospitalization and length of stay was reported from EINSTEIN DVT and PE studies. As notable variations in practice between regions exist,[21] data from only North America was considered. Data from Ontario Case Costing Initiative (OCCI)[22] were used to assign length of stay (LOS); data on overall LOS from EINSTEIN were not used, as a large number of non-Canadian sites participated and LOS lacked face validity (as judged by Canadian clinical experts). Opinions from Canadian experts were also obtained (Table 13).

Table 13: Index Venous Thromboembolism Management

	Proportion Admitted (Range)	Length of Stay, days (range)	References
DVT	19% (0% to 40%)	6.7(5 to 8)	van Bellen,[21] OCCI[22]
	30%	3	Expert opinion
PE	67% (30% to 75%)	7.8 (6 to 9)	van Bellen,[21] OCCI[22]
	65%	2	Expert opinion

DVT = deep vein thrombosis; OCCI = Ontario Case Costing Initiative; PE = pulmonary embolism.

Differences in LOS by treatment strategy were reported only from the EINSTEIN studies, which found no difference in LOS for DVT in North American patients, but a small statistically significant reduction in LOS for patients with PE receiving rivaroxaban (compared with LMWH/VKA) of approximately 0.91 (95% CI, 0.87 to 0.95) of the LOS of LMWH/VKA.[21] This was applied in the base case for all DOACs.

Duration of LMWH administration was estimated to be seven days (median duration from trials included in NMA is 6.5 to 8 days) in the VKA strategy, as well as the DOACs that are initiated concomitantly with LMWH. Outpatient LMWH administration was assumed to be performed by patients or their caregivers; however, a proportion of patients may not be able to self-administer and require home-care administration, estimated at 19%.[23]

Monitoring

VKA requires monitoring of INR and dose titration, and typically this is most intensive during initiation and stabilization of the dose. This largely consists of physician consultations and laboratory testing, and in many jurisdictions a specific fee code for INR interpretation and dose adjustment can be used (in addition to or instead of a physician consultation visit). While specialized anticoagulation clinics and point-of-care testing is available in some regions, it is estimated by clinical experts that > 95% of anticoagulation monitoring occurs in primary care settings.

While Canadian data are available for anticoagulation (VKA) monitoring resource utilization,[24] most of the patients are on anticoagulation for a different indication (atrial fibrillation) and there is an absence of detail on initiation of treatment where monitoring intensity is greatest. As such, Canadian expert opinion was obtained to estimate usual care (Table 14). An additional scenario was constructed using opinion from family physicians, who reported greater frequency of monitoring activity (tested in scenario analysis). The unit costs are provided in Table 15.

Table 14: Monitoring in Reference Case (Family Physician Scenario in Parentheses)

	Months 0 to 3	Months 4 to 6	Months 6+
Number of INR tests (over 3 months)	8 (12)	3 (5)	1 (1)
INR interpretation and dose adjustment fee* (over 3 months	3 (3)	3 (3)	1 (3)
Physician visits (over 3 months) DOAC	3 (3)	1 (1)	0.25 (0.25)
VKA	3 (6)	1 (2)	0.5 (1)

DOAC = direct oral anticoagulants; INR = international normalized ratio; VKA = vitamin K antagonist.
* Fee may be used monthly (Ontario).

Venous Thromboembolism Management

Health care resource utilization for index VTE event managed as either an outpatient or in-patient was determined from OCCI data[22] (2010-2011 fiscal year inflated to 2014 Canadian dollar values), typical diagnostic tests, and resource utilization reported in previously published economic evaluations of VTE (Table 15).[23] Resource utilization was assumed to be similar for both the index and recurrent events.

Complications

Sources enumerating resource utilization for complications including major intracranial hemorrhage, major extracranial hemorrhage (assumed to be gastrointestinal bleed), CRNM bleed, PTS, and CTEPH were obtained from available literature and primary costing sources, with preference to Canadian data. These are shown in Table 15.

Costs

All costs are reported in 2014-2015 Canadian dollars, detailed in Table 15. Costs were inflated using the Consumer Price Index to 2014-2015.[25] Where appropriate, unit costs of resources consumed were obtained from Canadian sources, including OCCI[22] and Ontario Schedule of Benefits. Literature was used to inform costs of ICH and long-term management costs of PTS, and CTEPH (see table below for references). Resource use and costs from US sources[26] were converted to 2014-2015 Canadian dollars using the Bank of Canada exchange rate and Consumer Price Index.

Table 15: Cost Data

Variable Description	Base Estimate	Probability Distribution	Reference
Events			
DVT — IP DVT as most responsible diagnosis (6.7-day LOS) In-patient physician First Follow-up (per day) Specialist outpatient visit	$9,819 $8,905 $157/visit $105.25/visit $157	Triangular (± 25%)	 OCCI OSB OSB Code A615 OSB
DVT — OP 1 Doppler ultrasound 1 GP visit 1 specialist consultation 2 specialist follow-up 2 complete blood counts	$759 $292/test $77.2/visit $157/visit $105.25/visit $11.18/test	Triangular (± 25%)	 OCCI OSB OSB OSB BC payment schedule
PE — IP PE as most responsible diagnosis (7.8-day LOS) In-patient visit First Follow-up (per day) Specialist outpatient visit	$8,084 $7,054 $157/visit $105.25/visit $157/visit	Triangular (±25%)	 OCCI OSB OSB OSB
PE — OP ER visit ER physician fee 1 ventilation perfusion lung scan (50%) 1 spiral CT scan (50%) 1 GP visit 1 specialist consultation 2 specialist follow-up 2 complete blood counts	$1,513 $399 $97.60 $529/test $559/test $77.2/visit $157/visit $105.25/visit $10.96/test	Triangular (± 25%)	 OCCI; OSB OCCI; OSB OCCI; OSB OCCI; OSB OSB OSB OSB OSB
CRNM bleed ER visit ER physician fee	 $285 $97.60	Triangular (± 25%)	 OCCI OSB
EC bleed (cost of GI hemorrhage treatment)	$5,514	Triangular (± 25%)	OCCI (ICD-10 CA code K922)
IC bleed (acute treatment cost of hemorrhagic stroke: initial hospitalization and follow-up costs)	$17,288	Triangular (± 25%)	CADTH; Goeree (2005)[27]
PTS	$7,437	Triangular (± 25%)	Caprini (2003)[26]
CTEPH (PTE surgery 56.8%)	$83,102		Rubens (2007)[28]
Long-term costs (per annum)			
PTS CTEPH	$3,264	Triangular (± 25%)	Caprini (2003) OSB

Variable Description	Base Estimate	Probability Distribution	Reference
(warfarin monitoring + specialist visits) Post IC bleed	$1,524 $8,243		 CADTH (2012)[29] Goeree (2009)[27]
Monitoring costs			
INR test INR interpretation and VKA management fee Physician visit	$12.31 $12.75 $77.2	Triangular (± 50%) for the reference case and (± 25%) for the FP scenario	BC payment schedule OSB (G271) OSB

CRNM = clinically relevant non-major; CT = computerized tomography; CTEPH = chronic thromboembolic pulmonary hypertension; DVT = deep vein thrombosis; EC = extracranial; ER = emergency room; FP=family practitioner; GI = gastrointestinal; GP = general practitioner; IC = intracranial; INR = international normalized ratio; IP = in-patient; LOS = length of stay; OCCI = Ontario Case Costing Initiative; OP = outpatient; OSB = Ontario Schedule of Benefits; PE = pulmonary embolism; PTS = postthrombotic syndrome; VKA = vitamin K antagonist; PTE: pulmonary thrombo-endarterectomy
* Based on specific code for PE.
** As no specific code captures various type of minor bleeding, the cost is based on the average cost of the 50 most common ER visits.

Sensitivity Analyses

Deterministic Sensitivity Analysis

A wide range of univariate sensitivity analyses was conducted to test the effect of changes in underlying parameter values and assumptions within the models. These include the following:

Drug utilization:

- range of duration of LMWH use 5 to 10 days
- reduction in cost of DOAC by 10% to 50%
- proportion of patients who cannot self-inject to 0%
- mix of LMWH 60% enoxaparin, 25% dalteparin, 5% tinzaparin (estimated Canadian utilization)
- reduction of cost of LMWH by 50% (potential for generic entrants; however, generic brands have not yet been introduced).

VTE event:

- reduction in LOS for both DVT and PE (0.91 of baseline)
- reduction in probability of admission for VTE by 25% to 50%
- reduction in LOS to Canadian expert opinion (DVT: three days; PE: two days).

Monitoring costs:

- frequency of INR testing and interpretation 50% to 200%.

Baseline probabilities:

- upper and lower ranges of variance for each parameter.

Efficacy:

- point estimate and range of credible interval (informed by NMA)
- hazard ratio of major bleed applies to CRNM bleeds
- alternate approach to calculating hazard ratio to adjust for “zero” events

- assumption that all DOACs have similar efficacy and safety (pooled hazard ratio of recurrent VTE and major bleeding of DOAC versus LMWH/VKA)
- increased risk of DVT (only) in extended treatment with rivaroxaban (NMA shows no difference in overall VTE, but increased risk of DVT but not PE).

Quality of life:

- upper and lower ranges of estimates; if none available, vary by + 25%.

Additional Sensitivity and Scenario Analysis

A series of scenario analyses was also conducted, focusing on resource utilization for the index VTE event as well as monitoring. These include:

- Recurrent VTE treated with VKA: The reference case assumes recurrent VTE is treated with the original treatment. A policy option may include restricting DOAC for short-term use, with VKA being used for extended treatment.
- Family physician estimated monitoring: There is a lack of consensus on frequency of monitoring, and it is possible that clinical experts in VTE would perform less frequent monitoring than primary care practitioners. A sensitivity analysis considering increased frequency as informed by a primary care physician was also considered (Table 13). Further assessment of this considered 115% and 125%, which encompasses costs as determined from a Canadian study (primarily of patients with atrial fibrillation).[24]

Probabilistic Sensitivity Analysis

Probabilistic sensitivity analysis was conducted using a Monte Carlo simulation. For the simulation, probability distributions related to natural history parameters, hazard ratios, resource utilization (costs), and utilities were incorporated into the analysis.

Analysis adopted standard methods for defining uncertainty around parameters. Transition probabilities were characterized by beta and normal distributions and relative risks, and odds ratios were characterized by lognormal distributions. Utility decrements were characterized by normal distributions.

Estimates of incremental costs and QALYs were obtained by re-running the model employing values from the related probability distributions. In this study, 5,000 replications were conducted — i.e., a set of 5,000 outcome estimates was obtained. Cost-effectiveness acceptability curves were derived that present the probability that each treatment is optimal given different values of willingness to pay for an additional QALY.

Model Validation

Adhering to best practices for conducting economic evaluations,[8,30] before analyzing the results of the economic model, it was ensured that the results were logically plausible (made sense) and could be explained intuitively. The model was also assessed for logical inconsistencies by evaluating it under hypothetical conditions. The mathematical calculations were confirmed to be accurate and consistent with the specifications of the model (internal validity). It was determined that the model had predictive validity by comparing model outputs (a function of input variables and model structure) with outcomes from studies in the systematic review.

Results

Model Validation

Model validation results are shown in Table 16. Internal validity was demonstrated by comparing model predicted values with the informing estimates. External validity was assessed by comparing recurrent VTE and death at 10 years. Schulman[9] and Prandoni[10] estimate a range of recurrent VTE of 29% to 50%, which is similar to what was reported by the model that predicted 43% to 44%. Further, mortality at 10 years is reported to be 28.5%,[9] similar to the model predicted value of 30%. Table 16a reports the estimated percentage of patients that experience a major bleed during extended therapy treatment over one year, outlining the absolute and relative differences between treatment strategies.

Table 16: Probabilities Used in Model (Standard Therapy)

Variable Description	Literature Estimate	Lower 95% CI	Upper 95% CI	Reference	Model Predicted Value
Probability of rVTE (on tx) 3 mo 6 mo 12 mo	 0.010 0.020 0.0094	 0.009 0.018 0.0027	 0.011 0.022 0.0363	NMA	 0.0091 to 0.0103 0.0187 to 0.021 0.0059 to 0.0106
Probability of IC bleed 3 mo 6 mo 12 mo	 0.0008 0.0015 NA	 0.0004 0.0009 NA	 0.0012 0.0023 NA	NMA	 0.0007 to 0.0011 0.0023 to 0.0029 NA
Probability of major bleed 3 mo 6 mo 12 mo	 0.0068 0.0136 0.0120	 0.0059 0.0119 0.0051	 0.0078 0.0156 0.0305	NMA	 0.006 to 0.0071 0.0138 to 0.0152 0.0114 to 0.0157
Probability of death at 10 years 3 mo 6 mo Extended					 0.302 0.302 0.291
Probability of rVTE at 10 years 3 mo 6 mo					 0.441 0.434

CI = confidence interval; IC = intracranial; mo = month; NA = not assessed; NMA = network meta-analysis; rVTE = recurrent venous thromboembolism; tx = (please define).

Table 16a: Proportion of Patients With Major Bleeding (Extended Therapy) by Treatment Over One Year

	LMWH/ VKA	Apixaban 5 mg	Apixaban 2.5 mg	Rivaroxaban	Edoxaban & Dabigatran
Proportion with major bleed	1.20%	0.114%	0.26%	8.03%	1.20%

LMWH = low-molecular-weight heparin; VKA = vitamin K antagonist.

Three-Month Treatment — Reference Case

The incremental cost and cost-effectiveness of alternate strategies for the treatment of VTE for three months is presented in Table 17; the incremental costs, QALYs, and ICUR for each DOAC compared with LMWH/VKA are presented in Table 18.

Compared with LMWH/VKA, DOACs are associated with an incremental cost of $3,120 to $7,442 and incremental QALYs of –0.12 to 0.02 (Table 18). The incremental QALYs are driven by differences in the risk of major bleeding with extended therapy for those patients who develop recurrent VTE and require long-term anticoagulation therapy. ICURs of DOACs compared with LMWH/VKA range from dominated (more costly with similar benefit as LMWH/VKA) — apixaban, edoxaban, dabigatran — to $170,000 (apixaban 5 mg) to $206,000 (apixaban 2.5 mg) per QALY gained.

When considering sequential ICURs among DOACs (Table 17), compared with apixaban 5 mg, all other DOACs are associated with greater costs and result in slightly fewer QALYs.

Table 17: Three-Month Treatment — Sequential Incremental Cost-Utility Ratio

Strategy	Cost ($)	Incremental Cost ($)	QALYs	Incremental QALYs	ICUR ($/QALY)
LMWH/VKA	**9,566**	**0**	**8.8935**	**-**	**-**
APX5	12,686	3,120	8.9118	0.01830	170,481
APX2.5	12,782	96	8.9091	–0.002658	(Dominated by APX5)
EDX	13,685	999	8.8935	–0.01830	(Dominated by APX5)
DBG	13,685	999	8.8935	–0.01830	(Dominated by APX5)
RVX	17,007	4,322	8.7766	–0.1352	(Dominated by APX 5)

APX2.5 = apixaban 2.5 mg; APX5 = apixaban 5 mg; DBG = dabigatran; EDX = edoxaban; ICUR = incremental cost-utility ratio; LMWH = low-molecular-weight heparin; QALY = quality-adjusted life-year; RVX = rivaroxaban; VKA = vitamin K antagonist.

Table 18: Three-Month Treatment Incremental Cost-Utility Ratio — Direct Oral Anticoagulants Compared With Low-Molecular-Weight Heparin/Vitamin K Antagonist

Strategy	Cost ($)	Incremental Cost ($)	QALYs	Incremental QALYs	ICUR ($/QALY)
LMWH/VKA	**9,566**	**-**	**8.8935**	**-**	**-**
APX5	12,685	3,120	8.9118	0.0183	170,481
APX2.5	12,782	3,216	8.9091	0.0156	205,622
DBG	13,685	4,120	8.8935	0	(Dominated)
EDX	13,685	4,120	8.8935	0	(Dominated)
RVX	17,007	7,442	8.7766	–0.117	(Dominated)

APX2.5 = apixaban 2.5 mg; APX5 = apixaban 5 mg; DBG = dabigatran; EDX = edoxaban; ICUR = incremental cost-utility ratio; LMWH = low-molecular-weight heparin; QALY = quality-adjusted life-year; RVX = rivaroxaban; VKA = vitamin K antagonist.

Cost categories are presented in Table 19. Note that the majority of drug acquisition costs occur after the 3-month treatment period, as patients who develop recurrent VTE are re-initiated on the original anticoagulant treatment for long-term duration. The slightly lower costs for the index event are for assumed reductions in LOS for PE; long-term costs differ due to the varying hazard ratio of the risk of major bleeding (lower for apixaban, greater for rivaroxaban).

Table 19: Disaggregate Costs ($) for Three-Month Treatment Model

Strategy	3-Month Drug Cost	Lifelong Drug Cost	Monitoring Cost	Index VTE Costs	Event Costs (Excluding Index)	Long-Term Costs
LMWH/VKA	303	692	1,552	3,957	2,936	429
APX5	330	5,887	568	3,695	2,436	100
APX2.5	330	5,883	567	3,695	2,488	148
RVX	328	5,116	559	3,695	5,133	2,454
DBG	544	6,238	528	3,695	2,795	429
EDX	544	6,238	528	3,695	2,795	429

APX2.5 = apixaban 2.5 mg; APX5 = apixaban 5 mg; DBG = dabigatran; EDX = edoxaban; LMWH = low-molecular-weight heparin; RVX = rivaroxaban; VKA = vitamin K antagonist; VTE = venous thromboembolism.
Note: Three-month drug acquisition costs are also included in lifelong drug costs. Index costs include in-patient or outpatient diagnosis and management of VTE. Event costs include costs of recurrent VTE, bleeding, and other events including CTEPH. Long-term costs include chronic resource use associated with ICH and PTS.

Scenario Analyses — Three-Month Treatment

Scenario A: All Recurrent Venous Thromboembolism Treated With Vitamin K Antagonist

In this scenario, all patients with recurrent VTE are treated with VKA regardless of the initial treatment for the index VTE event. Incremental costs, QALYs, and ICUR are shown in Table 20; results anchored to LMWH/VKA are in Table 21, and selected cost categories are in Table 22.

Table 20: Three-Month Treatment Incremental Cost-Utility Ratio — Recurrent Venous Thromboembolism Treated With Vitamin K Antagonist

Strategy	Cost ($)	Incremental Cost ($)	QALYs	Incremental QALYs	ICUR ($/QALY)
APX5	9,115	0	8.8935	-	-
APX2.5	9,115	0	8.8935	-	-
RVX	9,122	7	8.8935	0	Dominated (by APX5/2.5)
EDX	9,291	176	8.8935	0	Dominated (by APX5/2.5)
DBG	9,291	176	8.8935	0	Dominated (by APX5/2.5)
LMWH/VKA	9,566	451	8.8935	0	Dominated (by APX5/2.5)

APX2.5 = apixaban 2.5 mg; APX5 = apixaban 5 mg; DBG = dabigatran; EDX = edoxaban; LMWH = low-molecular-weight heparin; QALY = quality-adjusted life-year; RVX = rivaroxaban; VKA = vitamin K antagonist.

Table 21: Three-Month Treatment Incremental Cost-Utility Ratio — Recurrent Venous Thromboembolism Treated With Vitamin K Antagonist (DOAC Compared With LMWH/VKA)

Strategy	Cost ($)	Incremental Cost ($)	QALYs	Incremental QALYs	ICUR ($/QALY)
LMWH/VKA	**9,566**	**-**	**8.8935**	**-**	**Reference**
APX5	9,115	–451	8.8935	0	Dominant
APX2.5	9,115	–451	8.8935	0	Dominant
RVX	9,122	–444	8.8935	0	Dominant
DBG	9,291	–275	8.8935	0	Dominant
EDX	9,291	–275	8.8935	0	Dominant

APX2.5 = apixaban 2.5 mg; APX5 = apixaban 5 mg; DBG = dabigatran; DOAC = direct oral anticoagulant; EDX = edoxaban; LMWH = low-molecular-weight heparin; QALY = quality-adjusted life-year; RVX = rivaroxaban; VKA = vitamin K antagonist; VTE = venous thromboembolism.

Table 22: Selected Cost Categories for Three-Month Treatment — Recurrent Venous Thromboembolism Treated With Vitamin K Antagonist

Strategy	3-month Drug Cost	Lifelong Drug Cost	Monitoring Cost	Index VTE Costs	Event Costs (Excluding Index)	Long-Term Costs
LMWH/VKA	303	692	1,552	3,957	2,936	429
APX5	329	718	1,478	3,695	2,795	429
APX2.5	329	718	1,478	3,695	2,795	429
RVX	335	725	1,478	3,695	2,795	429
DBG	544	933	1,478	3,695	2,795	429
EDX	544	933	1,478	3,695	2,795	429

APX2.5 = apixaban 2.5 mg; APX5 = apixaban 5 mg; DBG = dabigatran; EDX = edoxaban; LMWH = low-molecular-weight heparin; RVX = rivaroxaban; VKA = vitamin K antagonist; VTE = venous thromboembolism.

There are no differences in efficacy and safety during the three-month treatment (all hazard ratios cross unity), nor are there any differences in safety and efficacy for recurrent VTE and its treatment, as all patients are treated with VKA and there is no difference in QALYs. Total costs are lower for all DOACs compared with LMWH/VKA in this scenario, as the larger drug acquisition costs of short-term DOAC use compared with VKA are outweighed by lower monitoring costs, cost of LMWH, and less costly index events (assuming shorter LOS with DOAC compared with LMWH/VKA).

Sensitivity Analyses — Three-Month Treatment

Selected results of sensitivity analysis are shown in Table 23 for the reference case. Other sensitivity analyses had minimal impact on the ICUR or conclusions, including range of utility values for each of the health states, ranges of 95% CI for hazard ratio, probability of recurrent VTE, and blend of LMWH use in Canada (see Appendix). Sensitivity analysis was also performed on Scenario A, where all recurrent VTE are treated with VKA. In this case, given the similar QALYs among strategies, total costs were compared.

Selected parameters and their results are presented here. As apixaban 5 mg had a lower ICUR compared with other DOACs, results focus on this drug.

- Price reduction: The ICUR for apixaban 5 mg is $100,000, $75,000, $50,000, and $25,000 at 77.5%, 70%, 62%, and 54%, respectively, of the original price. Apixaban 2.5 mg is similar (72%, 65%, 58%, and 51%, respectively).
- Admission: If DOACs decrease the need for admission for treatment and management of the index event, the ICUR for apixaban is lower. Note that this has not been demonstrated in randomized controlled trials (RCTs), and that a relatively large reduction is required to have a significant impact on the ICUR.
- Monitoring costs: There is uncertainty and variability regarding the resource intensity associated with VKA monitoring. Doubling the reference case monitoring costs, or using the family physician scenario, results in ICURs of $85,661 and $96,778 for apixaban 5 mg versus LMWH/VKA. A sensitivity analysis that uses family physician monitoring cost, and then 110% of this (to simulate long-term monitoring costs from Schulman),[24] results in ICURs of $96,778 and $80,924, respectively.
- Risk of major bleeding: If the upper 95% CI of the risk of major bleeding is used, the ICUR is $47,771 (apixaban 5 mg versus LMWH/VKA); use of the lower CI increased the ICUR to $463,000.
- Shorter time horizon: This results in a very large ICUR, with much lower incremental benefit. This highlights that the QALY gains with apixaban are driven by reduction of major bleeding events that occur over a long time horizon.
- Use of point estimates: If point estimates from the NMA are used (instead of assumption of 1.0 if not statistically significant, see Table 7 and Table 8) the ICUR for DOACs is > $200,000 for all (including apixaban). This is due to the increase in recurrent VTE with attendant costs and complications.

Sensitivity analysis that used alternative approach to determine the hazard ratio of major bleeding did not alter conclusions. Pooling of all DOACs into one class for all hazard ratios led to ICURs of $320,000 to $420,000 compared with LMWH/VKA.

Sensitivity analysis on the scenario where recurrent VTE are treated with LMWH/VKA regardless of initial treatment strategy indicated that DOACs remained cost-saving compared with LMWH/VKA in all scenarios. Sensitivity analyses of long-term treatment factors were not assessed, as these are not relevant to this scenario.

Table 23: Three-Month Treatment Sensitivity Analysis (Compared With Low-Molecular-Weight Heparin/Vitamin K Antagonist)

Sensitivity Analysis	Strategy	Reference Case ICUR ($/QALY)	Scenario A (VKA for All Recurrent VTE) Incremental Cost ($)
Reference Case	**APX5** **APX2.5** **RVX** **DBG** **EDX**	**170,481** **205,622** **Dominated** **Dominated** **Dominated**	**–451** **–451** **–444** **–275** **–275**
DOAC drug costs reduced by 10%	APX5 APX2.5 RVX DBG EDX	139,018 168,832 Dominated Dominated Dominated	–483 –483 –477 –299 –299
DOAC drug costs reduced by 20%	APX5 APX2.5 RVX DBG EDX	107,555 132,043 Dominated Dominated Dominated	–515 –515 –510 –324 –324
DOAC drug costs reduced by 30%	APX5 APX2.5 RVX DBG EDX	76,092 95,253 Dominated Dominated Dominated	–547 –547 –543 –349 –349
DOAC drug costs reduced by 40%	APX5 APX2.5 RVX DBG EDX	44,629 58,463 Dominated Dominated Dominated	–580 –580 –576 –373 –373
DOAC drug costs reduced by 50%	APX5 APX2.5 RVX DBG EDX	13,166 21,674 Dominated Dominated Dominated	–612 –612 –608 –398 –398
Decrease admission for VTE by 25% for DOAC	APX5 APX2.5 RVX DBG EDX	114,914 140,612 Dominated Dominated Dominated	–1,468 –1,468 –1,461 –1,292 –1,292
Decrease admission for VTE by 50% for DOAC	APX5 APX2.5 RVX DBG EDX	59,348 75,603 Dominated Dominated Dominated	–2,485 –2,485 –2,478 –2,308 –2,308
VKA monitoring costs doubled	APX5 APX2.5 RVX DBG EDX	85,661 106,388 Dominated Dominated dominated	–755 –755 –748 –579 –579

Sensitivity Analysis	Strategy	Reference Case ICUR ($/QALY)	Scenario A (VKA for All Recurrent VTE) Incremental Cost ($)
Family physician VKA monitoring costs	APX5 APX2.5 RVX DBG EDX	96,778 119,382 Dominated Dominated Dominated	–683 –683 –676 –507 –507
Family physician VKA monitoring costs at 110%	APX5 APX2.5 RVX DBG EDX	80,924 100,846 Dominated Dominated Dominated	–737 –737 –730 –560 –560
Family physician VKA monitoring costs at 125%	APX5 APX2.5 RVX DBG EDX	57,146 73,026 Dominated Dominated Dominated	–817 –817 –811 –641 –641
LMWH reduced by 50%	APX5 APX2.5 RVX DBG EDX	182,251 219,393 Dominated Dominated Dominated	–311 –311 –304 –275 –275
Hazard ratio of major bleed also applies to CRNM bleed	APX5 APX2.5 RVX DBG EDX	156,144 191,076 Dominated Dominated Dominated	NA
Alternate approach to estimating hazard ratio for major bleeding (extended treatment)	APX5 APX2.5 RVX DBG EDX	153,096 170,851 Dominated 391,249 Dominated	NA
Hazard ratio of extended treatment major bleeding by "pooling" all DOACs (hazard ratio 0.56; 95% CI, 0.28 to 0.84)	APX5 APX2.5 RVX DBG EDX	383,007 383,007 320,181 420,248 420,248	NA
Point estimates for all hazard ratios (acute and extended, rVTE, and major bleeding)	APX5 APX2.5 RVX DBG EDX	216,238 268,326 Dominated 456,128 4,849,247	NA
Lower CI of major bleed (long-term) 0.0051	APX5 APX2.5 RVX DBG EDX	462,997 547,525 Dominated Dominated Dominated	NA
Upper CI of major bleed (long-term) 0.03045	APX5 APX2.5 RVX DBG EDX	47,771 62,192 Dominated Dominated Dominated	NA

Sensitivity Analysis	Strategy	Reference Case ICUR ($/QALY)	Scenario A (VKA for All Recurrent VTE) Incremental Cost ($)
Lower 95% CI for hazard ratio of major bleed (long-term)	APX5 APX2.5 RVX DBG EDX	149,666 151,558 Dominated 214,028 Dominated	NA
Upper 95% CI for hazard ratio of major bleed (long-term)	APX5 APX2.5 RVX DBG EDX	279,842 1,493,189 Dominated Dominated Dominated	NA
5-year time horizon	APX5 APX2.5 RVX DBG EDX	516,661 643,694 Dominated Dominated Dominated	NA

APX2.5 = apixaban 2.5 mg; APX5 = apixaban 5 mg; CI = confidence interval; CRNM = clinically relevant non-major; DBG = dabigatran; DOAC = direct oral anticoagulant; EDX = edoxaban; ICUR = incremental cost-utility ratio; LMWH = low-molecular-weight heparin; NA = not assessed; QALY = quality-adjusted life-year; rVTE = recurrent venous thromboembolism; RVX = rivaroxaban; VKA = vitamin K antagonist; VTE = venous thromboembolism.

Six-Month Treatment — Reference Case

The incremental cost and cost-effectiveness of alternate strategies for the treatment of VTE for six months is presented in Table 24; the incremental costs, QALYs, and ICUR for each DOAC compared with LMWH/VKA are presented in Table 25. Selected cost categories are shown in Table 26. Results follow a similar pattern as for the three-month treatment scenario, although acute treatment drug costs and monitoring are greater due to the increased duration of initial treatment.

Table 24: Six-Month Treatment Incremental Cost-Utility Ratio

Strategy	Cost ($)	Incremental Cost ($)	QALYs	Incremental QALYs	ICUR ($/QALY)
LMWH/VKA	9,765	-	8.8873	-	-
APX5	12,999	3,233	8.9048	0.01754	184,380
APX2.5	13,092	93	8.9023	–0.002547	Dominated (by APX5)
EDX	13,972	973	8.8873	–0.01754	Dominated (by APX5)
DBG	13,972	973	8.8873	–0.01754	Dominated (by APX5)
RVX	17,136	4,138	8.7752	–0.1296	Dominated (by APX5)

APX2.5 = apixaban 2.5 mg; APX5 = apixaban 5 mg; DBG = dabigatran; EDX = edoxaban; ICUR = incremental cost-utility ratio; LMWH = low-molecular-weight heparin; QALY = quality-adjusted life-year; RVX = rivaroxaban; VKA = vitamin K antagonist.

Table 25: Six-Month Treatment Incremental Cost-Utility Ratio (Direct Oral Anticoagulants Compared With Low-Molecular-Weight Heparin/Vitamin K Antagonist)

Strategy	Cost ($)	Incremental Cost ($)	QALYs	Incremental QALYs	ICUR ($/QALY)
LMWH/VKA	9,765	-	8.8873	-	-
APX5	12,999	3,233	8.9048	0.01754	184,380
APX2.5	13,092	3,326	8.9023	0.01499	221,922
EDX	13,972	4,207	8.8873	0	Dominated
DBG	13,972	4,207	8.8873	0	Dominated
RVX	17,136	7,371	8.7752	–0.1121	Dominated

APX2.5 = apixaban 2.5 mg; APX5 = apixaban 5 mg; DBG = dabigatran; EDX = edoxaban; ICUR = incremental cost-utility ratio; LMWH = low-molecular-weight heparin; QALY = quality-adjusted life-year; RVX = rivaroxaban; VKA = vitamin K antagonist.

Table 26: Selected Cost Categories for Six-Month Treatment

Strategy	6-month Drug Cost	Lifelong Drug Cost	Monitoring Cost	Index VTE Costs	Event Costs (Excluding Index)	Long-Term Costs
LMWH/VKA	316	695	1,661	3,957	2,966	487
APX5	639	6,023	631	3,694	2,478	171
APX2.5	639	6,020	631	3,694	2,529	217
EDX	852	6,372	592	3,695	2,826	487
DBG	852	6,372	592	3,695	2,826	487
RVX	603	5,293	623	3,695	5,093	2,431

APX2.5 = apixaban 2.5 mg; APX5 = apixaban 5 mg; DBG = dabigatran; EDX = edoxaban; LMWH = low-molecular-weight heparin; RVX = rivaroxaban; VKA = vitamin K antagonist; VTE = venous thromboembolism.
Note: Three-month drug acquisition costs are also included in lifelong drug costs. Index costs include in-patient or outpatient diagnosis and management of VTE. Event costs include costs of recurrent VTE, bleeding, and other events including CTEPH. Long-term costs include chronic resource use associated with ICH and PTS.

Similar to the three-month treatment model, small differences in QALYs and long-term costs among DOACs are driven by the hazard ratio of major bleeding compared with VKA, where only statistically significant differences (versus VKA) were assigned a value that varied from unity. While RVX has the lowest drug acquisition costs among DOACs, it also has the largest long-term costs due to increased risk of major bleeding.

Scenario Analyses — Six-Month Treatment

Scenario A: All Recurrent Venous Thromboembolism Treated With Vitamin K Antagonist

In this scenario, after the initial six-month treatment period, any recurrent VTE was treated with VKA long-term, regardless of the initial treatment. Results are shown in Table 27 and Table 28, and costs in Table 29. In this scenario, RVX is the least costly treatment strategy, and all DOAC treatment is less costly than LMWH/VKA.

Table 27: Six-Month Treatment Incremental Cost-Utility Ratio — Recurrent Venous Thromboembolism Treated With Vitamin K Antagonist

Strategy	Cost ($)	Incremental Cost ($)	QALYs	Incremental QALYs	ICUR ($/QALY)
RVX	9,511	-	8.8873	-	-
APX5	9,538	27	8.8873	0	Dominated (by RVX)
APX2.5	9,538	27	8.8873	0	Dominated (by RVX)
EDX	9,714	203	8.8873	0	Dominated (by RVX)
DBG	9,714	203	8.8873	0	Dominated (by RVX)
LMWH/VKA	9,765	254	8.8873	0	Dominated (by RVX)

APX2.5 = apixaban 2.5 mg; APX5 = apixaban 5 mg; DBG = dabigatran; EDX = edoxaban; ICUR = incremental cost-utility ratio; LMWH = low-molecular-weight heparin; QALY = quality-adjusted life-year; RVX = rivaroxaban; VKA = vitamin K antagonist.

Table 28: Six-Month Treatment Incremental Cost-Utility Ratio — Recurrent Venous Thromboembolism Treated With Vitamin K Antagonist (DOAC compared with LMWH/VKA)

Strategy	Cost ($)	Incremental Cost ($)	QALYs	Incremental QALYs	ICUR ($/QALY)
LMWH/VKA	9,765	0	8.8873	-	Reference
RVX	9,511	–254	8.8873	0	Dominant
APX5	9,538	–227	8.8872	0	Dominant
APX2.5	9,538	–227	8.8873	0	Dominant
EDX	9,714	–51	8.8873	0	Dominant
DBG	9,714	–51	8.8873	0	Dominant

APX2.5 = apixaban 2.5 mg; APX5 = apixaban 5 mg; DBG = dabigatran; DOAC = direct oral anticoagulant; EDX = edoxaban; ICUR = incremental cost-utility ratio; LMWH = low-molecular-weight heparin; QALY = quality-adjusted life-year; RVX = rivaroxaban; VKA = vitamin K antagonist.

Table 29: Selected Cost Categories for Six-Month Treatment — Recurrent Venous Thromboembolism Treated With Vitamin K Antagonist

Strategy	6-Month Drug Cost	Lifelong Drug Cost	Monitoring Cost	Index VTE Costs	Event Costs (Excluding Index)	Long-Term Costs
LMWH/VKA	316	695	1,661	3,957	2,966	487
RVX	610	989	1,514	3,695	2,826	487
APX5	638	1,017	1,514	3,695	2,826	487
APX2.5	638	1,017	1,514	3,695	2,826	487
EDX	852	1,231	1,475	3,695	2,826	487
DBG	852	1,231	1,475	3,695	2,826	487

APX2.5 = apixaban 2.5 mg; APX5 = apixaban 5 mg; DBG = dabigatran; EDX = edoxaban; LMWH = low-molecular-weight heparin; QALY = quality-adjusted life-year; RVX = rivaroxaban; VKA = vitamin K antagonist; VTE = venous thromboembolism.

Sensitivity Analysis — Six-Month Treatment

Selected results of sensitivity analysis are shown in Table 30 for the reference case. In general, trends were similar to the three-month treatment sensitivity analyses; many sensitivity analyses had minimal impact on results, including range of quality-of-life scores for each of the health states, ranges of 95% CI for hazard ratio, probability of recurrent VTE, and blend of LMWH use in Canada. The baseline risk of bleeding had a significant impact, along with DOAC drug costs. Selected sensitivity analysis was also conducted on the scenario where recurrent VTE was treated with VKA, demonstrating cost savings with DOACs compared with LMWH/VKA in all scenarios.

Selected parameters and their results are presented below. As apixaban 5 mg had a lower ICUR compared with other DOACs, results focus on this drug.

- Price reduction: The ICUR for apixaban 5 mg is $100,000, $75,000, $50,000, and $25,000 at 75%, 68%, 60%, and 53%, respectively, of the original price. Apixaban 2.5 mg is similar (69%, 63%, 56%, and 50%, respectively).
- Admission: If DOACs decrease the need for admission for treatment and management of the index event, the ICUR for apixaban is lower. Note that this has not been demonstrated in RCTs, and that a relatively large reduction is required to have a significant impact on the ICUR.
- Monitoring costs: There is uncertainty and variability regarding the resource intensity associated with VKA monitoring. Doubling the reference case monitoring costs, or using the family physician scenario, results in ICURs of $89,637 and $103,825 for apixaban 5 mg versus LMWH/VKA. Using 110% of the family physician scenario results in an ICUR of $86,295.

- Risk of major bleeding: If the upper 95% CI of the risk of major bleeding is used, the ICUR is $53,301 (apixaban 5 mg versus LMWH/VKA); use of the lower CI increased the ICUR to $496,834.
- Shorter time horizon: This results in a very large ICUR, with much lower incremental benefit. This highlights that the QALY gains with apixaban are driven by reduction of major bleeding events that occur over a long time horizon.
- Use of point estimates: If point estimates from the NMA are used (instead of assumption of 1.0 if not statistically significant, see Table 7 and Table 8), the ICUR for DOACs is > $160,000 for all (including apixaban). This is due to the increase in recurrent VTE with attendant costs and complications.

Sensitivity analysis that used the alternate approach to calculate the hazard ratio of major bleeding did not alter conclusions. Pooling of all DOACs into one class for all hazard ratios led to ICURs of $340,000 to $450,000 compared with LMWH/VKA.

Sensitivity analysis on the scenario where recurrent VTE are treated with LMWH/VKA regardless of initial treatment strategy indicated that DOACs remained cost-saving compared with LMWH/VKA in all scenarios. Sensitivity analyses that assessed long-term treatment factors were not assessed, as these are not relevant to this scenario.

Table 30: Six-Month Treatment Sensitivity Analysis (Compared With Low-Molecular-Weight Heparin/Vitamin K Antagonist)

Sensitivity Analysis	Strategy	Reference Case ICUR ($/QALY)	Scenario A (VKA for All Recurrent VTE) Incremental Cost ($)
Reference	**APX5** **APX2.5** **RVX** **DBG** **EDX**	**184,380** **221,921** **Dominated** **Dominated** **Dominated**	**–227** **–227** **–254** **–51** **–51**
DOAC drug costs reduced by 10%	APX5 APX2.5 RVX DBG EDX	150,788 182,642 Dominated Dominated Dominated	–289 –289 –314 –105 –105
DOAC drug costs reduced by 20%	APX5 APX2.5 RVX DBG EDX	117,196 143,362 Dominated Dominated Dominated	–351 –351 –373 –161 –161
DOAC drug costs reduced by 30%	APX5 APX2.5 RVX DBG EDX	83,605 104,083 Dominated Dominated Dominated	–414 –414 –433 –215 –215
DOAC drug costs reduced by 40%	APX5 APX2.5 RVX DBG EDX	50,013 64,804 Dominated Dominated Dominated	–477 –477 –493 –270 –270
DOAC drug costs reduced by 50%	APX5 APX2.5 RVX DBG EDX	16,422 25,524 Dominated Dominated Dominated	–539 –539 –552 –325 –325
Decrease admission for VTE by 25% for DOAC	APX5 APX2.5 RVX DBG EDX	126,529 154,241 Dominated Dominated Dominated	–1,242 –1,242 –1,269 –1,065 –1,065
Decrease admission for VTE by 50% for DOAC	APX5 APX2.5 RVX DBG EDX	68,678 86,560 Dominated Dominated Dominated	–2,256 –2,256 –2,283 –2,080 –2,080
VKA monitoring costs doubled	APX5 APX2.5 RVX DBG EDX	89,637 111,089 Dominated Dominated Dominated	–679 –679 –707 –503 –503
Family physician monitoring scenario	APX5 APX2.5 RVX DBG EDX	103,825 127,678 Dominated 266,070 Dominated	–559 –559 –586 –382 –382

Sensitivity Analysis	Strategy	Reference Case ICUR ($/QALY)	Scenario A (VKA for All Recurrent VTE) Incremental Cost ($)
Family physician monitoring scenario at 110%	APX5 APX2.5 RVX DBG EDX	86,295 107,170 Dominated Dominated Dominated	–637 –637 –664 –460 –460
Family physician monitoring scenario at 125%	APX5 APX2.5 RVX DBG EDX	60,000 76,407 Dominated Dominated Dominated	–754 –754 –781 –578 –578
LMWH reduced by 50%	APX5 APX2.5 RVX DBG EDX	196,563 236,175 Dominated Dominated Dominated	–367 –367 –394 –51 –51
Hazard ratio of major bleed also applies to CRNM bleed	APX5 APX2.5 RVX DBG EDX	168,811 207,131 Dominated Dominated Dominated	NA
Alternate approach to estimating hazard ratio for major bleeding (extended treatment)	APX5 APX2.5 RVX DBG EDX	165,806 184,776 Dominated 419,040 Dominated	NA
Hazard ratio of extended treatment major bleeding by “pooling” all DOACs (hazard ratio 0.56; 95% CI, 0.28 to 0.84)	APX5 APX2.5 RVX DBG EDX	411,427 411,427 344,103 449,939 449,939	NA
Point estimates for all hazard ratios (acute and extended, rVTE, and major bleeding)	APX5 APX2.5 RVX DBG EDX	167,872 198,883 Dominated 356,649 2,537,070	NA
Lower CI of major bleed (long-term) 0.0051	APX5 APX2.5 RVX DBG EDX	496,834 587,129 Dominated Dominated Dominated	NA
Upper CI of major bleed (long-term) 0.03045	APX5 APX2.5 RVX DBG EDX	53,301 68,719 Dominated Dominated Dominated	NA
Lower 95% CI for hazard ratio of major bleed (long-term)	APX5 APX2.5 RVX DBG EDX	162,142 164,163 Dominated 230,203 Dominated	NA

Sensitivity Analysis	Strategy	Reference Case ICUR ($/QALY)	Scenario A (VKA for All Recurrent VTE) Incremental Cost ($)
Upper 95% CI for hazard ratio of major bleed (long-term)	APX5 APX2.5 RVX DBG EDX	301,213 1,501,330 Dominated Dominated Dominated	NA
5-year time horizon	APX5 APX2.5 RVX DBG EDX	1,309,834 1,576,746 Dominated Dominated Dominated	NA

APX2.5 = apixaban 2.5 mg; APX5 = apixaban 5 mg; CI = confidence interval; CRNM = clinically relevant non-major; DBG = dabigatran; DOAC = direct oral anticoagulant; EDX = edoxaban; ICUR = incremental cost-utility ratio; LMWH = low-molecular-weight heparin; NA = not assessed; QALY = quality-adjusted life-year; rVTE = recurrent venous thromboembolism; RVX = rivaroxaban; VKA = vitamin K antagonist; VTE = venous thromboembolism.

Extended (Lifelong) Treatment

The reference case results for treatment of index VTE with lifelong anticoagulation are shown in Table 31. Small clinical benefits are realized by a lower risk of major bleed with apixaban compared with VKA, however DOACs are associated with increased costs given the long-term use of medications with a large acquisition cost.

Table 31: Extended Treatment Incremental Cost-Utility Ratio

Strategy	Cost ($)	Incremental Cost ($)	QALYs	Incremental QALYs	ICUR ($/QALY)
LMWH/VKA	10,514	-	8.8445	-	-
APX5	19,063	8,549	8.8734	0.02887	296,113
APX2.5	19,182	119	8.8692	–0.00418	Dominated (by APX5)
EDX	20,029	965	8.8445	–0.0289	Dominated (by APX5)
DBG	20,029	965	8.8445	–0.0289	Dominated (by APX5)
RVX	23,926	4,863	8.6557	–0.2177	Dominated (by APX5)

APX2.5 = apixaban 2.5 mg; APX5 = apixaban 5 mg; DBG = dabigatran; EDX = edoxaban; ICUR = incremental cost-utility ratio; LMWH = low-molecular-weight heparin; QALY = quality-adjusted life-year; RVX = rivaroxaban; VKA = vitamin K antagonist.

Table 31a: Extended Treatment Incremental Cost-Utility Ratio (Direct Oral Anticoagulants Compared With Low-Molecular-Weight Heparin/Vitamin K Antagonist)

Strategy	Cost ($)	Incremental Cost ($)	QALYs	Incremental QALYs	ICUR ($/QALY)
LMWH/VKA	10,514	-	8.8445	-	Reference
APX5	19,063	8,549	8.8734	0.02887	296,113
APX2.5	19,182	8,668	8.8692	0.02469	351,094
EDX	20,029	9,514	8.8445	0	Dominated
DBG	20,029	9,514	8.8445	0	Dominated
RVC	23,926	13,411	8.6557	–0.1889	Dominated

APX2.5 = apixaban 2.5 mg; APX5 = apixaban 5 mg; DBG = dabigatran; EDX = edoxaban; ICUR = incremental cost-utility ratio; LMWH = low-molecular-weight heparin; QALY = quality-adjusted life-year; RVX = rivaroxaban; VKA = vitamin K antagonist.

Table 32: Selected Cost Categories for Extended Treatment

Strategy	Lifelong Drug Cost	Monitoring Cost	Index VTE Costs	Event Costs (Excluding Index)	Long-Term Costs
LMWH/VKA	808	2,968	3,957	2,637	145
APX5	12,469	1,025	3,695	1,841	34
APX2.5	12,461	1,025	3,695	1,953	50
EDX	12,597	981	3,695	2,611	145
DBG	12,597	981	3,695	2,611	145
RVX	10,759	1,000	3,695	7,600	871

APX2.5 = apixaban 2.5 mg; APX5 = apixaban 5 mg; DBG = dabigatran; EDX = edoxaban; LMWH = low-molecular-weight heparin; RVX = rivaroxaban; VKA = vitamin K antagonist; VTE = venous thromboembolism.
Note: Index costs include in-patient or outpatient diagnosis and management of VTE. Event costs include costs of recurrent VTE, bleeding, and other events including CTEPH. Long-term costs include chronic resource use associated with ICH and PTS.

Sensitivity Analysis — Extended Treatment

Selected sensitivity analyses on the reference case of extended treatment are presented in Table 33. ICURs are influenced in a similar manner to the three- and six-month models, although overall findings remain largely unchanged.

Table 33: Extended Treatment Sensitivity Analysis (Compared With Low-Molecular-Weight Heparin/Vitamin K Antagonist)

Sensitivity Analysis	Strategy	$/QALY (Compared With LMWH/VKA)
Reference	**APX5** **APX2.5** **EDX** **DBG** **RVX**	**296,113** **351,094** **Dominated** **Dominated** **Dominated**
DOAC drug costs reduced by 30%	APX5 APX2.5 EDX DBG RVX	169,402 203,018 Dominated Dominated Dominated
DOAC drug costs reduced by 40%	APX5 APX2.5 EDX DBG RVX	127,166 153,659 Dominated Dominated Dominated
DOAC drug costs reduced by 50%	APX5 APX2.5 EDX DBG RVX	84,929 153,659 Dominated Dominated Dominated
Decrease admission for VTE by 50% for DOAC	APX5 APX2.5 EDX DBG RVX	246,149 292,657 Dominated Dominated Dominated
VKA monitoring costs doubled	APX5 APX2.5 EDX DBG RVX	193,297 230,862 Dominated Dominated Dominated
Family physician monitoring scenario	APX5 APX2.5 EDX DBG RVX	192,873 230,366 Dominated Dominated Dominated
Family physician monitoring scenario 110%	APX5 APX2.5 EDX DBG RVX	172,267 206,270 Dominated Dominated Dominated
Family physician monitoring scenario 125%	APX5 APX2.5 EDX DBG RVX	141,359 170,126 Dominated Dominated Dominated
LMWH reduced by 50%	APX5 APX2.5 EDX DBG RVX	300,952 356,754 Dominated Dominated Dominated

Sensitivity Analysis	Strategy	$/QALY (Compared With LMWH/VKA)
Hazard ratio of major bleed also applies to CRNM bleed	APX5 APX2.5 EDX DBG RVX	260,479 308,472 Dominated Dominated Dominated
Alternate approach to estimating hazard ratio for major bleeding (extended treatment)	APX5 APX2.5 EDX DBG RVX	268,913 296,693 Dominated 596,431 Dominated
Hazard ratio of extended treatment major bleeding by “pooling” all DOACs (hazard ratio 0.56; 95% CI, 0.28 to 0.84)	APX5 APX2.5 EDX DBG RVX	628,635 628,635 638,744 638,744 Dominated
Point estimates for all hazard ratios (acute and extended, rVTE, and major bleeding)	APX5 APX2.5 EDX DBG RVX	583,468 794,988 7,165,086 739,508 Dominated
Lower CI of major bleed (long-term) 0.0051	APX5 APX2.5 EDX DBG RVX	757,150 889,971 Dominated Dominated Dominated
Upper CI of major bleed (long-term) 0.03045	APX5 APX2.5 EDX DBG RVX	102,685 125,007 Dominated Dominated Dominated
Lower 95% CI for hazard ratio of major bleed (long-term)	APX5 APX2.5 EDX DBG RVX	263,546 266,507 Dominated 337,841 Dominated
Upper 95% CI for hazard ratio of major bleed (long-term)	APX5 APX2.5 EDX DBG RVX	467,219 2,224,881 Dominated Dominated Dominated
5-year time horizon	APX5 APX2.5 EDX DBG RVX	3,384,947 4,008,996 Dominated Dominated Dominated

APX2.5 = apixaban 2.5 mg; APX5 = apixaban 5 mg; CI = confidence interval; CRNM = clinically relevant non-major; DBG = dabigatran; DOAC = direct oral anticoagulant; EDX = edoxaban; LMWH = low-molecular-weight heparin; QALY = quality-adjusted life-year; rVTE = recurrent venous thromboembolism; RVX = rivaroxaban; VKA = vitamin K antagonist; VTE = venous thromboembolism.

CADTH

Extended Treatment: Acetylsalicylic Acid Versus Low-Molecular-Weight Heparin/Vitamin K Antagonist

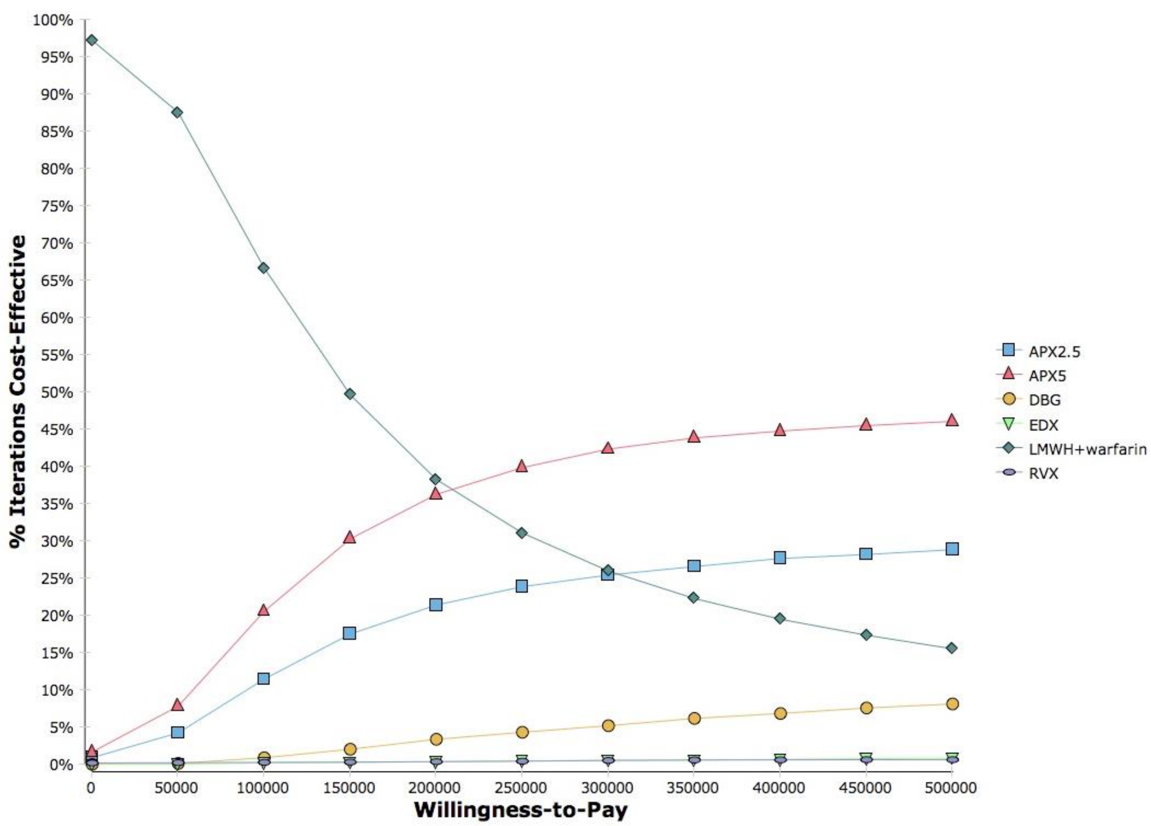
While both drug acquisition costs and monitoring are lower for ASA than VKA, treatment with ASA is associated with a greater risk of recurrent VTE, and no statistically significant difference in the risk of major bleeding. Due to the increased costs of additional VTE events, ASA is more costly ($62) and less effective (–0.096) than VKA.

In sensitivity analysis, when the family physician scenario of VKA monitoring was assessed, VKA was more costly (+$2587) and more effective (+0.5706 QALYs), leading to an ICUR of $4,534 for LMWH/VKA versus ASA. When the lower bound of the 95% CI for recurrent VTE for ASA was used (1.001), ASA was less costly ($–1,940) and equally efficacious; however, when the upper bound was used, ASA was more costly ($9,660) and less effective (–0.5706 QALYs).

Probabilistic Sensitivity Analysis

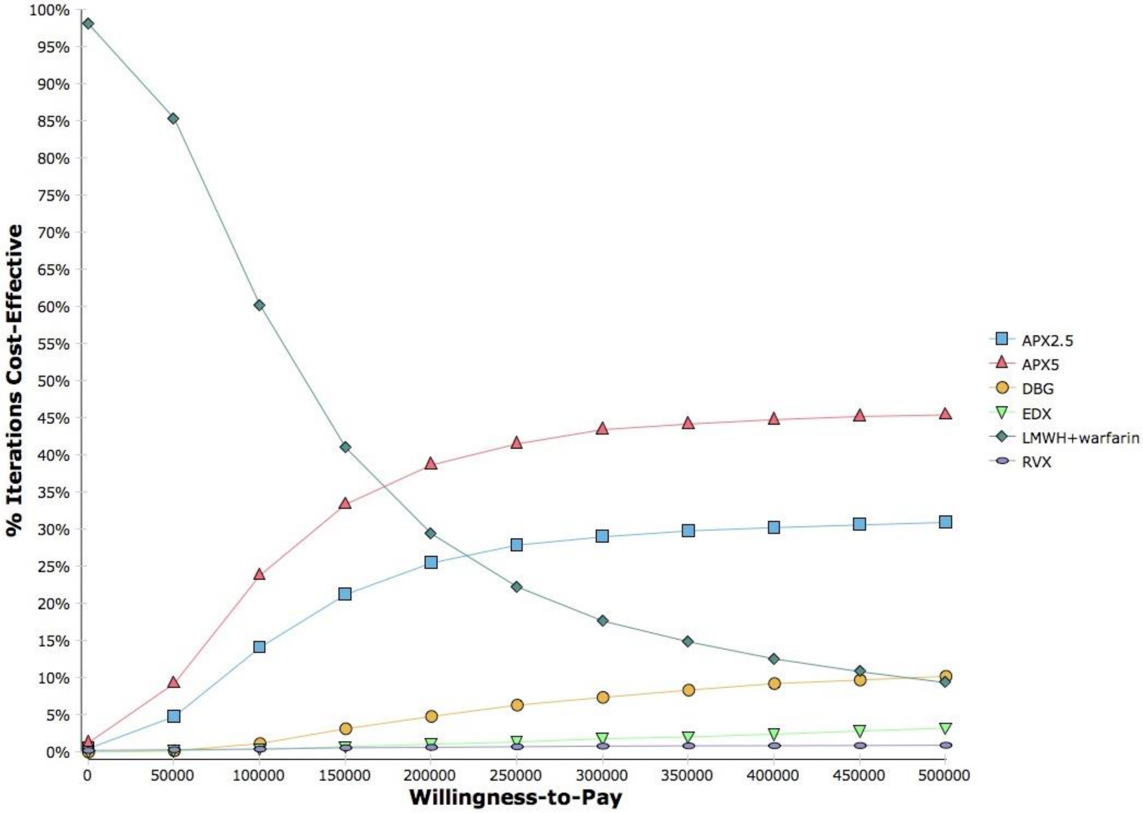
Cost-effectiveness acceptability curves for three-month, six-month, and lifetime treatment are shown in Figures 2, 3, and 4.

Figure 2: Cost-Effectiveness Acceptability Curve for Three-Month Treatment



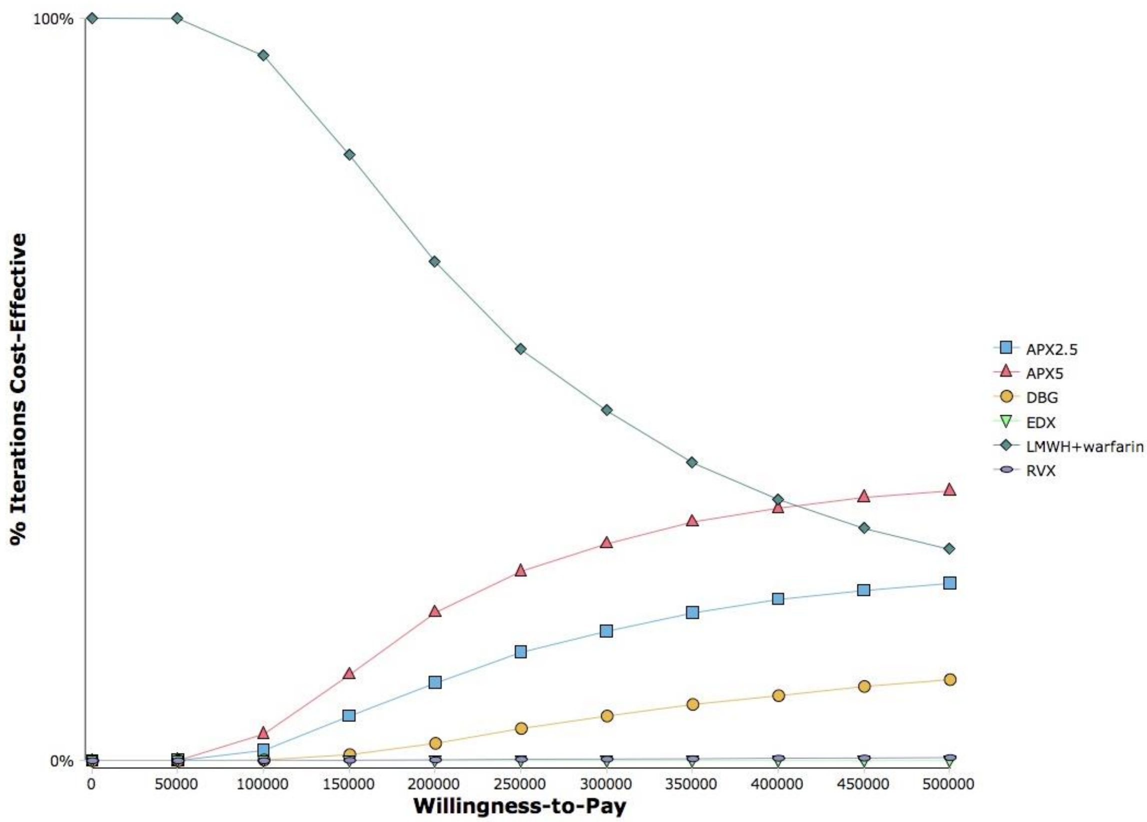
APX2.5 = apixaban 2.5 mg; APX5 = apixaban 5 mg; DBG = dabigatran; EDX = edoxaban; LMWH = low-molecular-weight heparin; RVX = rivaroxaban.

Figure 3: Cost-Effectiveness Acceptability Curve for Six-Month Treatment



APX2.5 = apixaban 2.5 mg; APX5 = apixaban 5 mg; DBG = dabigatran; EDX = edoxaban; LMWH = low-molecular-weight heparin; RVX = rivaroxaban.

Figure 4: Cost-Effectiveness Acceptability Curve for Lifetime Treatment



APX2.5 = apixaban 2.5 mg; APX5 = apixaban 5 mg; DBG = dabigatran; EDX = edoxaban; LMWH = low-molecular-weight heparin; RVX = rivaroxaban.

In the three- or six-month models, LMWH/VKA is the preferred strategy at willingness-to-pay thresholds of $175,000 to $200,000; above this, apixaban 5 mg becomes the preferred strategy. Other DOACs have a lower probability of being considered cost-effective compared with apixaban 5 mg at all willingness-to-pay values.

Similar results are observed when considering the family physician monitoring scenario (Appendix, Figure A1 and Figure A2), although the point where apixaban 5 mg becomes preferred over LMWH/VKA occurs at a lower willingness-to-pay threshold (~$100,000 to $125,000).

For lifetime treatment, LMWK/VKA is the preferred strategy until the willingness-to-pay value exceeds ~$400,000, at which point apixaban 5 mg is preferred. Similar to the three- and six-month models, apixaban 5 mg is more likely to be considered cost-effective than the other DOACs at all willingness-to-pay values.

In the scenario where all recurrent VTE is treated with LMWH/VKA regardless of initial treatment strategy, DOACs are preferable to LMWH/VKA at all willingness-to-pay values (Appendix A4 and A5). Apixaban is more likely to be the preferred strategy, followed by rivaroxaban, edoxaban, and dabigatran.

Discussion

The reference case analysis suggests that compared with LMWH/VKA, treatment with apixaban in patients with VTE is associated with ICURs of $170,000 per QALY gained, or greater. Other DOACs, including dabigatran, edoxaban, and rivaroxaban result in increased cost and QALY gains that are less than apixaban, when compared with LMWH/VKA (or in the case of rivaroxaban, fewer QALYs than LMWH/VKA). Incremental costs are largely driven by the greater drug acquisition cost of DOACs versus VKA. It should be noted that in the scenarios examining short-term treatment (three or six months), the majority of DOAC drug cost accrues after six months — this is due to the relatively common occurrence of recurrent VTE, which is typically treated with extended-duration anticoagulation therapy.

Gains in QALYs are achieved with apixaban due to the reduction in the risk of major bleeding when compared with VKA, although the absolute gain in QALYs is relatively small. It should be noted that many of the gains occur over a lengthy time horizon, as shown when considering a shorter time horizon of five years where incremental QALYs are much smaller, resulting in much higher ICURs than in the reference case. If the relative benefits of apixaban on major bleeding attenuate over time, the ICUR will be larger than estimated.

Limiting Use of Direct Oral Anticoagulants to Three or Six Months Only

If DOAC use is constrained to short duration of use (three to six months), and all subsequent anticoagulation for recurrent VTE is restricted to VKA, treatment with DOACs will likely result in cost savings. The significant drug acquisition cost of DOACs is outweighed by cost of LMWH/VKA treatment — namely the relatively high upfront cost of LMWH, greater monitoring costs with VKA, and small reduction in index hospitalization result in cost savings for DOACs. These cost savings in the short term are relatively robust in sensitivity analysis (explored in scenario assuming recurrent VTE treated with VKA). As all patients are treated with VKA for recurrent VTE, differences in efficacy and safety (and attendant impact on QALYs) among DOACs do not factor into this analysis. It should be noted that while this is a theoretical policy option, operationalizing this may be challenging. Patients and providers with previous experience with a DOAC may resist treatment with VKA, and may resist switching from a DOAC to VKA.

Among DOACs, there are small differences in drug treatment costs, due to the variable requirement for LMWH use with some DOACs, use of loading doses, as well as small differences in daily drug costs. In the scenario of treatment limited to three or six months, the relative attractiveness among DOACs was driven largely by drug acquisition costs and the cost of LMWH (if required). Note that while LMWH is off-patent, there are currently no generic products available (tested in sensitivity analysis with reduction in cost). At currently listed prices, apixaban and rivaroxaban are the least costly, although differences are small. Furthermore, this assumes that short-term use of rivaroxaban is not associated with an increased risk of major bleed (which may occur with long-term use as per the NMA), and that any future long-term anticoagulation would use VKA. It should be noted that a listed price for edoxaban is not yet available in Canada, and it may appear more attractive if priced lower. Finally, drug plan negotiations may lead to different costs that may alter relative attractiveness of DOACs.

Extended Treatment with Direct Oral Anticoagulants

Due to the relatively large drug acquisition costs of DOACs, longer-term treatment, either in patients initially treated for three or six months who have recurrent VTE, or cohorts of patients treated lifelong for the index VTE, incremental costs are substantially greater for DOACs compared with LMWH/VKA.

Extended therapy with apixaban is associated with a reduction in major bleeding; however, the QALYs gained with this safety benefit are quite small (0.02 to 0.03), the equivalent to an additional seven to 11 days of perfect health over a lifetime horizon. While the relative magnitude of benefit is relatively large (hazard ratio 0.10 or 0.23), the absolute benefit of apixaban versus VKA is small, as the long-term risk of major bleeding is relatively low, and intracranial bleeding that is responsible for the greatest morbidity and mortality is not common (see Table 16a for estimates of the proportion of patients who experience major bleeding by treatment strategy). The small difference in QALYs between apixaban and LMWH has implications for interpretation, as the ICUR tends to be much more unstable when the denominator (incremental QALYs) is small; as such, minor changes in cost may have a large impact on the ICUR in this situation.

Treatment of VTE with apixaban is associated with relatively large ICURs compared with LMWH/VKA. The ICUR becomes more attractive when the baseline risk of major bleed is larger; however, it should be noted that a patient population at high risk of bleeding has not been specifically studied (it is not established that a selected high-risk population would experience the same relative benefit). Of note, the model assumes continued relative efficacy over a lifetime time horizon; if efficacy attenuates over time, less benefit will be realized with apixaban compared with VKA.

The ICUR also becomes more attractive if monitoring costs of VKA are large. The family physician monitoring scenario assumes incremental monitoring costs of $424 in the first three months, $185 in the second three months, then annual incremental monitoring costs of $472 per year. The annual monitoring of VKA in Canada (stable, largely atrial fibrillation) is estimated to be $198 every three months,[24] and exclusion of costs that would occur in patients on either medication (family physician visits) results in annual incremental cost of VKA monitoring of $542; this is used as the maximum value in sensitivity in a previous CADTH publication.[29] The family physician monitoring scenario is similar to this, and is further approximated when family physician monitoring is increased to include this value (110% and 125% lead to incremental costs of monitoring of $526 and $608 per year).
Other DOACs appear less attractive, as they are associated with increased costs but no clinical benefit with respect to major bleeding or recurrent VTE using data from the NMA; rivaroxaban is associated with worse outcomes and costs compared with LMWH, given the increased risk of major bleeding associated with its use. However, there are methodological issues (see Clinical Review Report — NMA) and the credible intervals are very wide. An alternate approach to determining the hazard ratio of major bleeding is tested in sensitivity analysis, where there is no difference in major bleeding with extended use (credible interval [CrL] cross unity; however, this does not alter conclusions, as there is no clinical benefit compared with standard care.

Time in therapeutic range may have an impact on relative efficacy and safety. Unfortunately, data are not available to examine this. There has also been speculation that differential adherence may occur with VKA (requiring blood tests) compared with DOACs, which would have implications for both costs as well as relative efficacy.

There are other limitations of this analysis. First, efficacy and harms data were based on randomized controlled trial data, which have internal validity but may lack generalizability. Second, there is uncertainty around the robustness of the NMA results. There are relatively small numbers of patients, and many estimates were associated with large credible intervals and methodological uncertainty. If future studies alter conclusions regarding relative safety and efficacy, the cost effectiveness should be revisited. Also, several assumptions were necessary to conduct a full economic evaluation over a lifetime time horizon; however, extensive sensitivity analysis was conducted to harness these. Compliance with therapy, which may be of more concern with DOACs versus VKA, was not assessed as pragmatic data on frequency over time, and consequences are not clear.

In summary, restricted use of DOACs over a short time frame (three or six months) appears to be less costly than LMWH/VKA, and this result is robust in sensitivity analysis. However, treatment with DOACs over a long term (either at index VTE or after recurrent VTE) is associated with greater costs. DOACs that result in incremental clinical benefit (apixaban 5 mg or 2.5 mg twice daily) are associated with relatively large ICURs. The attractiveness of the ICUR may improve with significant reduction in the cost of DOACs, if monitoring costs of VKA are large, or if the risk of major bleeding is very high (although data on relative safety and efficacy in a subpopulation at high risk of bleeding is lacking). Other DOACs are less attractive for extended treatment given the lack of evidence of benefit (dabigatran and edoxaban) or suggestion of harm (rivaroxaban).

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Appendix A: Additional Sensitivity Analysis

Table A1: Three-Month Treatment — Additional Sensitivity Analysis

Sensitivity Analysis	Strategy	Reference Case ICUR ($/QALY)	Scenario A (VKA for All Recurrent VTE) Incremental Cost ($)
Reference Case	**APX5** **APX2.5** **RVX** **DBG** **EDX**	**170,481** **205,622** **Dominated** **Dominated** **Dominated**	**–451** **–451** **–444** **–275** **–275**
Nursing costs reduced to 0%	APX5 APX2.5 RVX DBG EDX	171,536 206,856 Dominated Dominated Dominated	–438 –438 –432 –275 –275
Mix of LMWH	APX5 APX2.5 RVX DBG EDX	172,027 207,431 Dominated Dominated Dominated	–433 –433 –426 –275 –275
DOAC reduced LOS for both DVT and PE	APX5 APX2.5 RVX DBG EDX	159,686 192,993 Dominated Dominated Dominated	–648 –648 –642 –472 –472
LMWH 5 days	APX5 APX2.5 RVX DBG EDX	177,207 213,491 Dominated Dominated Dominated	–371 –371 –364 –275 –275
VKA monitoring costs reduced by 50%	APX5 APX2.5 RVX DBG EDX	212,891 255,240 Dominated Dominated Dominated	–299 –299 –292 –122 –122
VKA monitoring costs reduced by 25%	APX5 APX2.5 RVX DBG EDX	191,686 230,431 Dominated Dominated Dominated	–375 –375 –368 –199 –199
VKA monitoring costs increased by 50%	APX5 APX2.5 RVX DBG EDX	128,072 157,321 Dominated Dominated Dominated	–603 –603 –596 –427 –427
rVTE on-treatment lower CI acute only 0.009	APX5 APX2.5 RVX DBG EDX	170,491 205,634 Dominated Dominated dominated	–451 –451 –444 –275 –275

Sensitivity Analysis	Strategy	Reference Case ICUR ($/QALY)	Scenario A (VKA for All Recurrent VTE) Incremental Cost ($)
rVTE on-treatment upper CI acute only 0.011	APX5 APX2.5 RVX DBG EDX	170,473 205,613 Dominated Dominated Dominated	–451 –451 –444 –275 –275
Major bleed lower CI acute only 0.0059	APX5 APX2.5 RVX DBG EDX	170,484 205,626 Dominated Dominated Dominated	–451 –451 –444 –275 –275
Major bleed upper CI acute only 0.0078	APX5 APX2.5 RVX DBG EDX	170,478 205,619 Dominated Dominated Dominated	–451 –451 –444 –275 –275
rVTE off-treatment lower CI 0.0213	APX5 APX2.5 RVX DBG EDX	170,709 205,945 Dominated Dominated Dominated	–435 –435 –428 –259 –259
rVTE off-treatment upper CI 0.0312	APX5 APX2.5 RVX DBG EDX	155,464 175,278 Dominated Dominated Dominated	–464 –464 –457 –288 –288
QoL DVT lower CI 0.55	APX5 APX2.5 RVX DBG EDX	170,482 205,623 Dominated Dominated Dominated	–451 –451 –444 –275 –275
QoL DVT upper CI 0.94	APX5 APX2.5 RVX DBG EDX	170,481 205,622 Dominated Dominated Dominated	–451 –451 –444 –275 –275
QoL PE lower CI 0.45	APX5 APX2.5 RVX DBG EDX	170,482 205,623 Dominated Dominated Dominated	–451 –451 –444 –275 –275
QoL PE upper CI 0.91	APX5 APX2.5 RVX DBG EDX	170,481 205,622 Dominated Dominated Dominated	–451 –451 –444 –275 –275
QoL PTS lower CI 0.76	APX5 APX2.5 RVX DBG EDX	170,481 205,623 Dominated Dominated Dominated	–451 –451 –444 –275 –275

Sensitivity Analysis	Strategy	Reference Case ICUR ($/QALY)	Scenario A (VKA for All Recurrent VTE) Incremental Cost ($)
QoL PTS upper CI 1.00	APX5 APX2.5 RVX DBG EDX	170,481 205,622 Dominated Dominated Dominated	–451 –451 –444 –275 –275
QoL EC bleed lower CI 0.15	APX5 APX2.5 RVX DBG EDX	170,181 205,260 Dominated Dominated Dominated	–451 –451 –444 –275 –275
QoL EC bleed upper CI 0.86	APX5 APX2.5 RVX DBG EDX	170,608 205,775 Dominated Dominated Dominated	–451 –451 –444 –275 –275
QoL IC bleed lower CI 0.00	APX5 APX2.5 RVX DBG EDX	169,558 204,509 Dominated Dominated Dominated	–451 –451 –444 –275 –275
QoL IC bleed lower CI 0.65	APX5 APX2.5 RVX DBG EDX	173,631 209,423 Dominated Dominated Dominated	–451 –451 –444 –275 –275
QoL post IC bleed lower CI 0.702	APX5 APX2.5 RVX DBG EDX	166,823 201,214 Dominated Dominated Dominated	–451 –451 –444 –275 –275
QoL post IC bleed lower CI 0.724	APX5 APX2.5 RVX DBG EDX	174,303 210,229 Dominated Dominated Dominated	–451 –451 –444 –275 –275
QoL CTEPH lower CI 0.528	APX5 APX2.5 RVX DBG EDX	170,491 205,623 Dominated Dominated Dominated	–451 –451 –444 –275 –275
QoL CTEPH lower CI 0.592	APX5 APX2.5 RVX DBG EDX	170,491 205,623 Dominated Dominated Dominated	–451 –451 –444 –275 –275
1-year time horizon	APX5 APX2.5 RVX DBG EDX	24,633,730 28,769,756 Dominated Dominated Dominated	–319 –319 –313 –143 –143

Sensitivity Analysis	Strategy	Reference Case ICUR ($/QALY)	Scenario A (VKA for All Recurrent VTE) Incremental Cost ($)
3-year time horizon	APX5 APX2.5 RVX DBG EDX	6,644,036 7,596,703 Dominated Dominated Dominated	–356 –356 –351 –180 –180
Discount rate 0%	APX5 APX2.5 RVX DBG EDX	178,615 215,490 Dominated Dominated Dominated	–505 –505 –497 –328 –328
Discount rate 3%	APX5 APX2.5 RVX DBG EDX	169,594 204,555 Dominated Dominated Dominated	–469 –469 –462 –293 –293

APX2.5 = apixaban 2.5 mg; APX5 = apixaban 5 mg; CI = confidence interval; CTEPH = chronic thromboembolic pulmonary hypertension; DBG = dabigatran; DOAC = direct oral anticoagulant; DVT = deep vein thrombosis; EC = extracranial; EDX = edoxaban; IC = intracranial; ICUR = incremental cost-utility ratio; LMWH = low-molecular-weight heparin; LOS = length of stay; PE = pulmonary embolism; PTS = postthrombotic syndrome; QALY = quality-adjusted life-year; QoL = quality of life; rVTE = recurrent venous thromboembolism; RVX = rivaroxaban; VKA = vitamin K antagonist; VTE = venous thromboembolism.

Table A2: Six-Month Treatment — Additional Sensitivity Analysis

Sensitivity Analysis	Strategy	Reference Case ICUR ($/QALY)	Scenario A (VKA for All Recurrent VTE) Incremental Cost ($)
Reference Case	**APX5** **APX2.5** **RVX** **DBG** **EDX**	**184,380** **221,921** **Dominated** **Dominated** **Dominated**	**–227** **–227** **–254** **–51** **–51**
Nursing costs reduced to 0%	APX5 APX2.5 RVX DBG EDX	185,471 223,199 Dominated Dominated Dominated	–215 –215 –242 –51 –51
Mix of LMWH	APX5 APX2.5 RVX DBG EDX	185,979 223,794 Dominated Dominated Dominated	–209 –209 –236 –51 –51
DOAC reduced LOS for both DVT and PE	APX5 APX2.5 RVX DBG EDX	173,142 208,775 Dominated Dominated Dominated	–424 –424 –452 –248 –248
LMWH 5 days	APX5 APX2.5 RVX DBG EDX	173,142 208,775 Dominated Dominated Dominated	–147 –147 –175 –51 –51
VKA monitoring costs reduced by 50%	APX5 APX2.5 RVX DBG EDX	231,751 277,343 Dominated Dominated Dominated	–0.76 –0.76 –28 –175 –175
VKA monitoring costs reduced by 25%	APX5 APX2.5 RVX DBG EDX	208,065 249,632 Dominated Dominated Dominated	–114 –114 –141 –62 –62
VKA monitoring costs increased by 50%	APX5 APX2.5 RVX DBG EDX	137,008 157,321 Dominated Dominated Dominated	–454 –454 –481 –277 –277
rVTE on-treatment lower CI acute only 0.009	APX5 APX2.5 RVX DBG EDX	184,404 221,950 Dominated Dominated dominated	–227 –227 –254 –51 –51
rVTE on-treatment upper CI acute only 0.011	APX5 APX2.5 RVX DBG EDX	184,359 221,897 Dominated Dominated Dominated	–227 –227 –254 –51 –51

Sensitivity Analysis	Strategy	Reference Case ICUR ($/QALY)	Scenario A (VKA for All Recurrent VTE) Incremental Cost ($)
Major bleed lower CI acute only 0.0059	APX5 APX2.5 RVX DBG EDX	184,384 221,927 Dominated Dominated Dominated	–227 –227 –254 –51 –51
Major bleed upper CI acute only 0.0078	APX5 APX2.5 RVX DBG EDX	184,375 221,916 Dominated Dominated Dominated	–227 –227 –254 –51 –51
rVTE off-treatment lower CI 0.0213	APX5 APX2.5 RVX DBG EDX	186,467 224,421 Dominated Dominated Dominated	–212 –212 –239 –35 –35
rVTE off-treatment upper CI 0.0312	APX5 APX2.5 RVX DBG EDX	182,355 219,503 Dominated Dominated Dominated	–240 –240 –267 –64 –64
QoL DVT lower CI 0.55	APX5 APX2.5 RVX DBG EDX	184,380 221,922 Dominated Dominated Dominated	–227 –227 –254 –51 –51
QoL DVT upper CI 0.94	APX5 APX2.5 RVX DBG EDX	184,379 221,922 Dominated Dominated Dominated	–227 –227 –254 –51 –51
QoL PE lower CI 0.45	APX5 APX2.5 RVX DBG EDX	184,380 221,922 Dominated Dominated Dominated	–451 –451 –444 –275 –275
QoL PE upper CI 0.91	APX5 APX2.5 RVX DBG EDX	184,379 221,922 Dominated Dominated Dominated	–227 –227 –254 –51 –51
QoL PTS lower CI 0.76	APX5 APX2.5 RVX DBG EDX	184,380 221,922 Dominated Dominated Dominated	–227 –227 –254 –51 –51
QoL PTS upper CI 1.00	APX5 APX2.5 RVX DBG EDX	184,379 221,922 Dominated Dominated Dominated	–227 –227 –254 –51 –51

Sensitivity Analysis	Strategy	Reference Case ICUR ($/QALY)	Scenario A (VKA for All Recurrent VTE) Incremental Cost ($)
QoL EC bleed lower CI 0.15	APX5	184,051	–227
	APX2.5	221,526	–227
	RVX	Dominated	–254
	DBG	Dominated	–51
	EDX	Dominated	–51
QoL EC bleed upper CI 0.86	APX5	184,518	–227
	APX2.5	222,089	–227
	RVX	Dominated	–254
	DBG	Dominated	–51
	EDX	Dominated	–51
QoL IC bleed lower CI 0.00	APX5	183,370	–227
	APX2.5	220,706	–227
	RVX	Dominated	–254
	DBG	Dominated	–51
	EDX	Dominated	–51
QoL IC bleed lower CI 0.65	APX5	187,827	–227
	APX2.5	226,072	–227
	RVX	Dominated	–254
	DBG	Dominated	–51
	EDX	Dominated	–51
QoL post IC bleed lower CI 0.702	APX5	180,421	–227
	APX2.5	217,161	–227
	RVX	Dominated	–254
	DBG	Dominated	–51
	EDX	Dominated	–51
QoL post IC bleed lower CI 0.724	APX5	188,516	–227
	APX2.5	226,896	–227
	RVX	Dominated	–254
	DBG	Dominated	–51
	EDX	Dominated	–51
QoL CTEPH lower CI 0.528	APX5	184,380	–227
	APX2.5	221,922	–227
	RVX	Dominated	–254
	DBG	Dominated	–51
	EDX	Dominated	–51
QoL CTEPH lower CI 0.592	APX5	184,380	–227
	APX2.5	221,922	–227
	RVX	Dominated	–254
	DBG	Dominated	–51
	EDX	Dominated	–51
1-year time horizon	APX5	16,174,156	–93
	APX2.5	18,883,266	–93
	RVX	Dominant	–121
	DBG	Dominated	83
	EDX	Dominated	83
3-year time horizon	APX5	-147,003	–131
	APX2.5	-276,483	–131
	RVX	504,998	–159
	DBG	Dominated	45
	EDX	Dominated	45

Sensitivity Analysis	Strategy	Reference Case ICUR ($/QALY)	Scenario A (VKA for All Recurrent VTE) Incremental Cost ($)
Discount rate 0%	APX5 APX2.5 RVX DBG EDX	188,405 226,998 Dominated Dominated Dominated	–278 –278 –305 –102 –102
Discount rate 3%	APX5 APX2.5 RVX DBG EDX	181,290 218,281 Dominated Dominated Dominated	–244 –244 –271 –68 –68

APX2.5 = apixaban 2.5 mg; APX5 = apixaban 5 mg; CI = confidence interval; CTEPH = chronic thromboembolic pulmonary hypertension; DBG = dabigatran; DOAC = direct oral anticoagulant; DVT = deep vein thrombosis; EC = extracranial; EDX = edoxaban; IC = intracranial; ICUR = incremental cost-utility ratio; LMWH = low-molecular-weight heparin; LOS = length of stay; PE = pulmonary embolism; PTS = postthrombotic syndrome; QALY = quality-adjusted life-year; QoL = quality of life; rVTE = recurrent venous thromboembolism; RVX = rivaroxaban; VKA = vitamin K antagonist; VTE = venous thromboembolism.

Table A3: Extended Treatment — Additional Sensitivity Analysis

Sensitivity Analysis	Strategy	$/QALY (Compared With LMWH/VKA)
Reference	**APX5** **APX2.5** **EDX** **DBG** **RVX**	**296,113** **351,094** **Dominated** **Dominated** **Dominated**
DOAC drug costs reduced by 10%	APX5 APX2.5 EDX DBG RVX	258,876 301,736 Dominated Dominated Dominated
DOAC drug costs reduced by 20%	APX5 APX2.5 EDX DBG RVX	211,639 252,377 Dominated Dominated Dominated
Nursing costs reduced to 0%	APX5 APX2.5 EDX DBG RVX	296,546 351,601 Dominated Dominated Dominated
Mix of LMWH	APX5 APX2.5 EDX DBG RVX	296,748 351,838 Dominated Dominated Dominated
Decrease admission for VTE by 25% for DOAC	APX5 APX2.5 EDX DBG RVX	271,126 321,876 Dominated Dominated Dominated
DOAC reduced LOS for both DVT and PE	APX5 APX2.5 EDX DBG RVX	291,331 345,503 Dominated Dominated Dominated
LMWH 5 days	APX5 APX2.5 EDX DBG RVX	298,878 354,328 Dominated Dominated Dominated
VKA monitoring costs reduced by 50%	APX5 APX2.5 EDX DBG RVX	347,521 411,210 Dominated Dominated Dominated
VKA monitoring costs reduced by 25%	APX5 APX2.5 EDX DBG RVX	321,817 381,152 Dominated Dominated Dominated

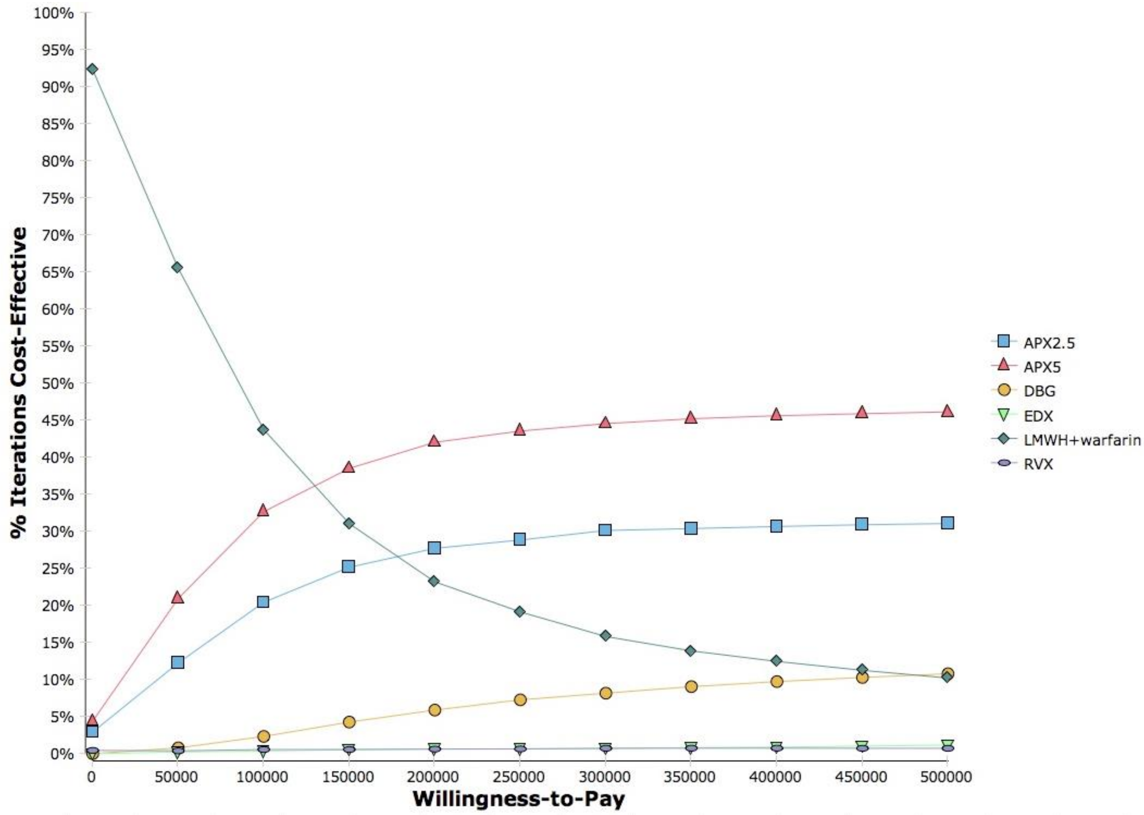
Sensitivity Analysis	Strategy	$/QALY (Compared With LMWH/VKA)
VKA monitoring costs increased by 50%	APX5 APX2.5 EDX DBG RVX	244,705 290,978 Dominated Dominated Dominated
rVTE on-treatment lower CI acute only 0.009	APX5 APX2.5 EDX DBG RVX	296,131 351,115 Dominated Dominated Dominated
rVTE on-treatment upper CI acute only 0.011	APX5 APX2.5 EDX DBG RVX	296,098 351,077 Dominated Dominated Dominated
Major bleed lower CI acute only 0.0059	APX5 APX2.5 EDX DBG RVX	296,116 351,098 Dominated Dominated Dominated
Major bleed upper CI acute only 0.0078	APX5 APX2.5 EDX DBG RVX	296,110 351,091 Dominated Dominated Dominated
rVTE off-treatment lower CI 0.0213	APX5 APX2.5 EDX DBG RVX	296,206 351,203 Dominated Dominated Dominated
rVTE off-treatment upper CI 0.0312	APX5 APX2.5 EDX DBG RVX	296,020 350,985 Dominated Dominated Dominated
QoL DVT lower CI 0.55	APX5 APX2.5 EDX DBG RVX	301,698 357,717 Dominated Dominated Dominated
QoL DVT upper CI 0.94	APX5 APX2.5 EDX DBG RVX	293,397 347,874 Dominated Dominated Dominated
QoL PE lower CI 0.45	APX5 APX2.5 EDX DBG RVX	300,963 356,844 Dominated Dominated Dominated

Sensitivity Analysis	Strategy	$/QALY (Compared With LMWH/VKA)
QoL PE upper CI 0.91	APX5 APX2.5 EDX DBG RVX	293,590 348,103 Dominated Dominated Dominated
QoL PTS lower CI 0.76	APX5 APX2.5 EDX DBG RVX	296,114 351,095 Dominated Dominated Dominated
QoL PTS upper CI 1.00	APX5 APX2.5 EDX DBG RVX	296,113 351,094 Dominated 337,841 Dominated
QoL EC bleed lower CI 0.15	APX5 APX2.5 EDX DBG RVX	295,401 350,250 Dominated Dominated Dominated
QoL EC bleed upper CI 0.86	APX5 APX2.5 EDX DBG RVX	296,413 351,450 Dominated Dominated Dominated
QoL IC bleed lower CI 0.00	APX5 APX2.5 EDX DBG RVX	293,928 348,504 Dominated Dominated Dominated
QoL IC bleed lower CI 0.65	APX5 APX2.5 EDX DBG RVX	303,636 360,013 Dominated Dominated Dominated
QoL post IC bleed lower CI 0.702	APX5 APX2.5 EDX DBG RVX	295,542 350,417 Dominated Dominated Dominated
QoL post IC bleed lower CI 0.724	APX5 APX2.5 EDX DBG RVX	296,686 351,774 Dominated Dominated Dominated
QoL CTEPH lower CI 0.528	APX5 APX2.5 EDX DBG RVX	296,113 351,094 Dominated Dominated Dominated

Sensitivity Analysis	Strategy	$/QALY (Compared With LMWH/VKA)
QoL CTEPH lower CI 0.592	APX5 APX2.5 EDX DBG RVX	296,113 351,094 Dominated Dominated Dominated
1-year time horizon	APX5 APX2.5 EDX DBG RVX	Dominated Dominated Dominated Dominated Dominated
3-year time horizon	APX5 APX2.5 EDX DBG RVX	Dominated Dominated Dominated Dominated Dominated
Discount rate 0%	APX5 APX2.5 EDX DBG RVX	298,808 354,318 Dominated Dominated Dominated
Discount rate 3%	APX5 APX2.5 EDX DBG RVX	285,144 338,101 Dominated Dominated Dominated

APX2.5 = apixaban 2.5 mg; APX5 = apixaban 5 mg; CI = confidence interval; CTEPH = chronic thromboembolic pulmonary hypertension; DBG = dabigatran; DOAC = direct oral anticoagulant; DVT = deep vein thrombosis; EC = extracranial; EDX = edoxaban; IC = intracranial; LMWH = low-molecular-weight heparin; LOS = length of stay; PE = pulmonary embolism; PTS = postthrombotic syndrome; QALY = quality-adjusted life-year; QoL = quality of life; rVTE = recurrent venous thromboembolism; RVX = rivaroxaban; VKA = vitamin K antagonist; VTE = venous thromboembolism.

Figure A1: Cost-Effectiveness Acceptability Curve for Family Physician Scenario and Three Months of Treatment



APX2.5 = apixaban 2.5 mg; APX5 = apixaban 5 mg; DBG = dabigatran; EDX = edoxaban; LMWH = low-molecular-weight heparin; RVX = rivaroxaban.

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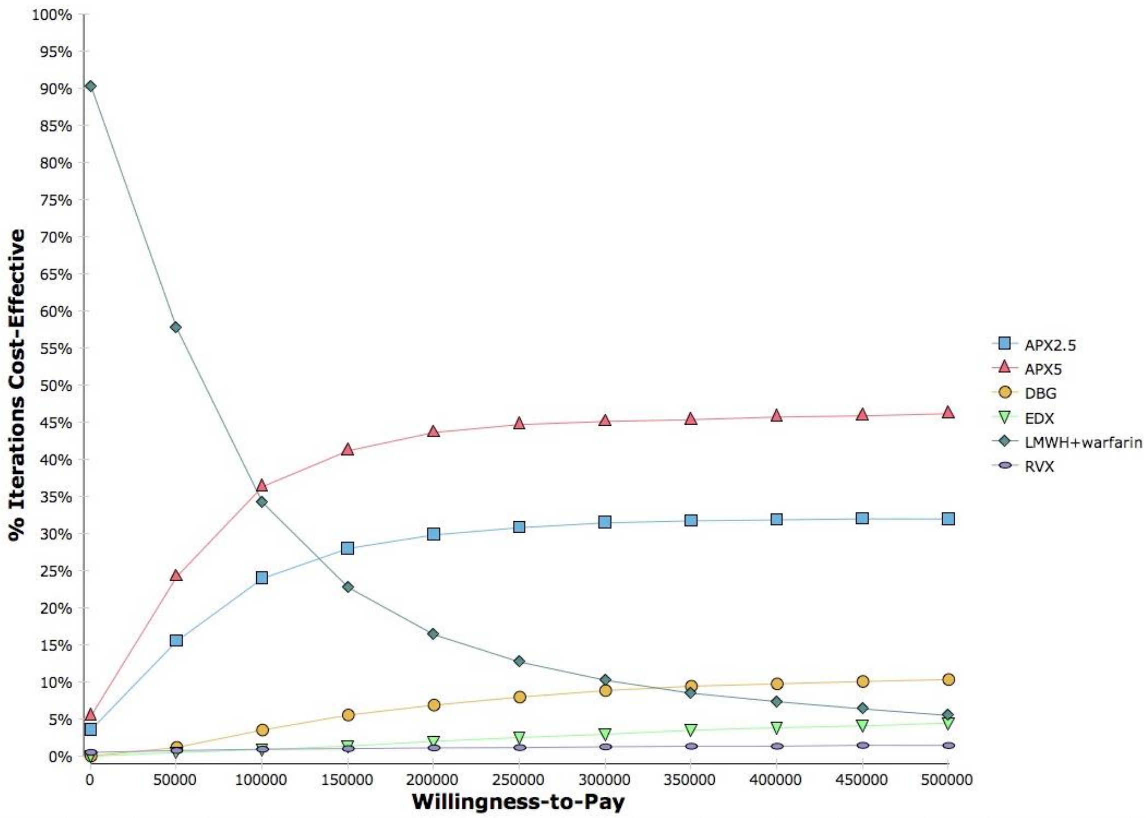
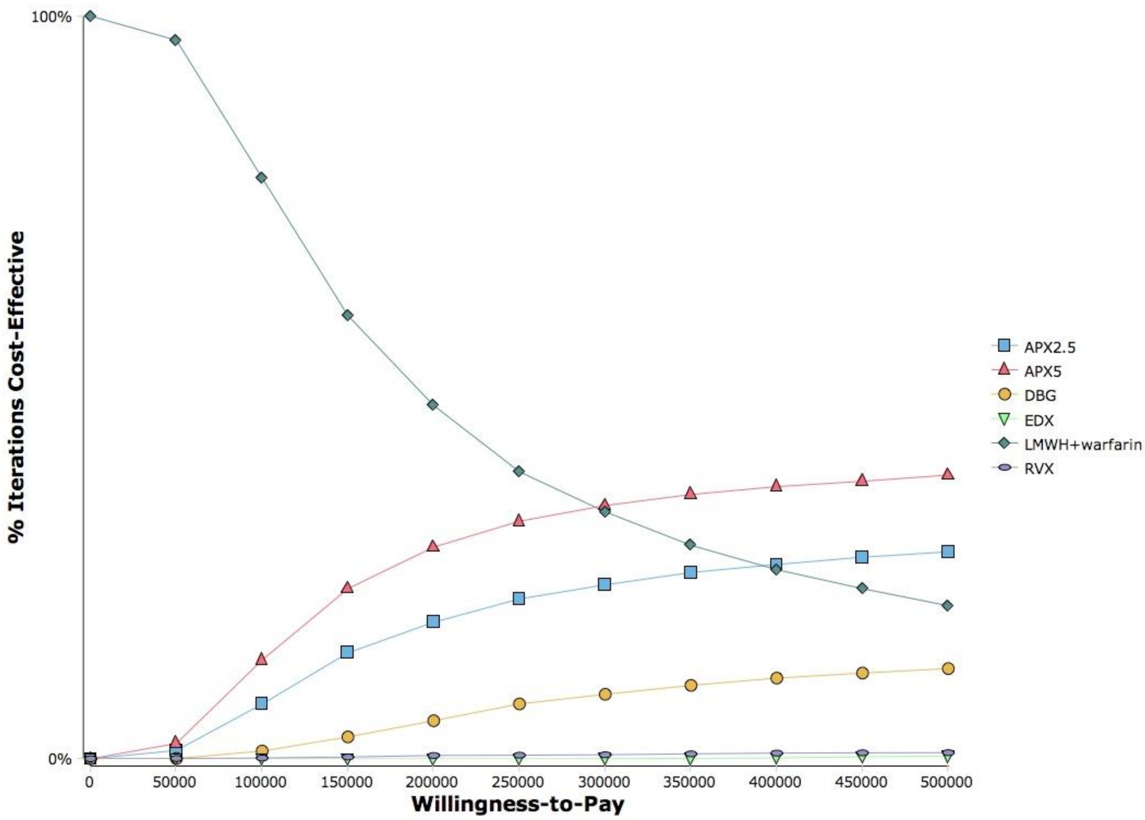
Figure A2: Cost-Effectiveness Acceptability Curve for Family Physician Scenario and Six Months of Treatment



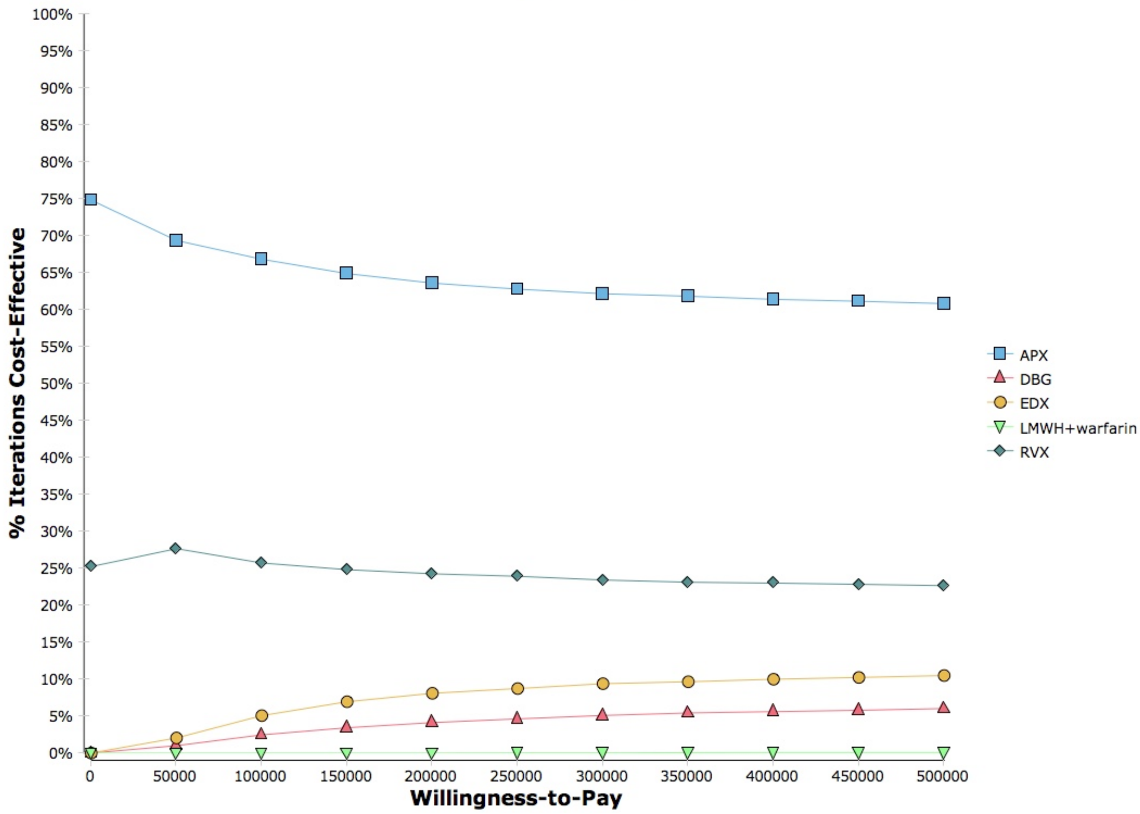
APX2.5 = apixaban 2.5 mg; APX5 = apixaban 5 mg; DBG = dabigatran; EDX = edoxaban; LMWH = low-molecular-weight heparin; RVX = rivaroxaban.

Figure A3: Cost-Effectiveness Acceptability Curve for Family Physician Scenario and Lifetime Treatment



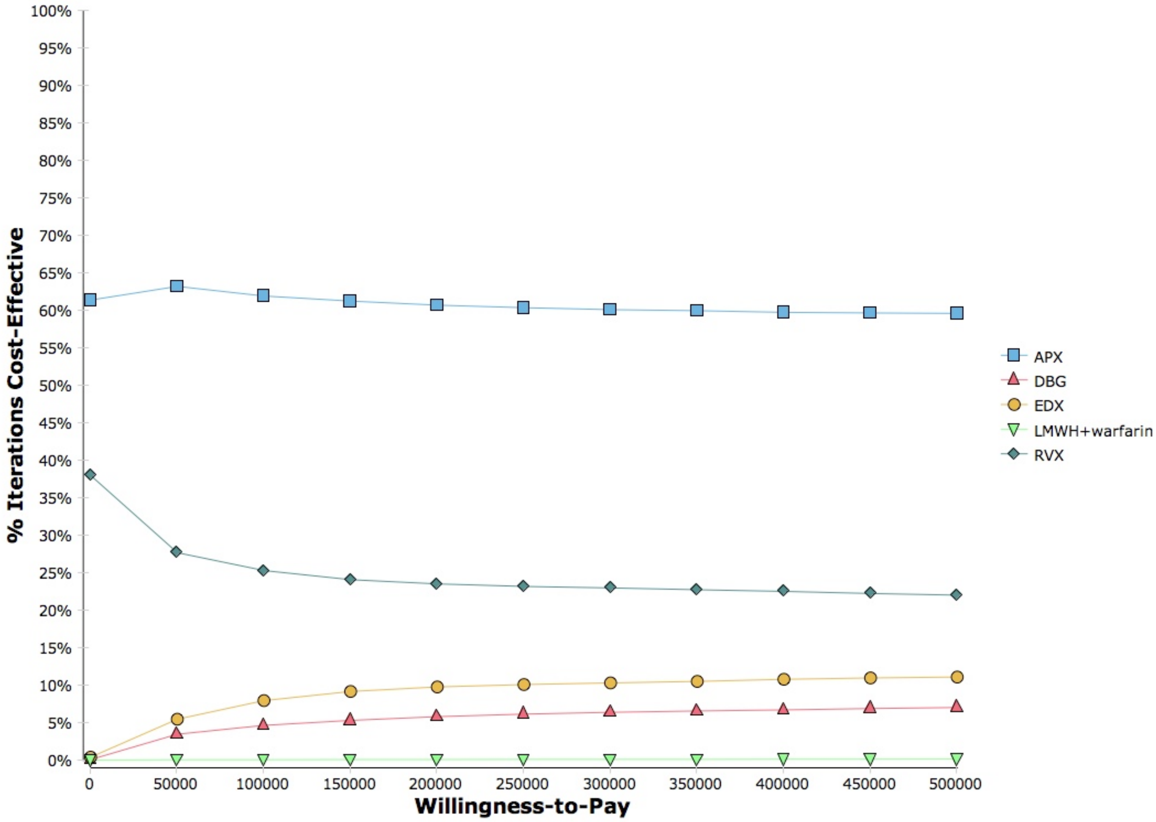
APX2.5 = apixaban 2.5 mg; APX5 = apixaban 5 mg; DBG = dabigatran; EDX = edoxaban; LMWH = low-molecular-weight heparin; RVX = rivaroxaban.

Figure A4: Cost-Effectiveness Acceptability Curve for Recurrent Venous Thromboembolism Treated With LMWH/VKA, Scenario and Three-Month Treatment



APX2.5 = apixaban 2.5 mg; APX5 = apixaban 5 mg; DBG = dabigatran; EDX = edoxaban; LMWH = low-molecular-weight heparin; RVX = rivaroxaban.

Figure A5: Cost-Effectiveness Acceptability Curve for Recurrent Venous Thromboembolism Treated With LMWH/VKA, Scenario and Six-Month Treatment



APX2.5 = apixaban 2.5 mg; APX5 = apixaban 5 mg; DBG = dabigatran; EDX = edoxaban; LMWH = low-molecular-weight heparin; RVX = rivaroxaban.